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PLASMA COLLOID OSMOTIC PRESSURE AS A FACTOR IN EDEMA FORMATION AND EDEMA ABSORPTION *

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THE proteins of the blood plasma being hydrophilic colloids in solution must exert an osmotic pressure. This osmotic pressure measures the momentum of the impacts made by the colloid particles on a unit of surface. Water and salt will pass from the outside to the inside of a tube whose wall is permeable to salt and water but is not permeable to colloid particles if there is a salt solution within the tube containing a hydrophilic colloid dispersed in it. Water and salt entering the tube increase the hydrostatic pressure of the fluid within it until this hydrostatic pressure exactly equals the colloid osmotic pressure. Water and salt will be filtered out of such a tube if the hydrostatic pressure within the tube is higher than the colloid osmotic pressure. This process is known as ultrafiltration and the filtration of water and salt proceeds until the concentration of the colloid within the tube is such as to determine a colloid osmotic pressure equal to the hydrostatic pressure.

The walls of the capillaries are ultrafilters. They allow salts and water to filter through them in both directions but in their normal state they tend to prevent the filtration of the plasma proteins across their walls. The permeability of an ultrafilter membrane can be changed so that it will allow not only water and salts through it but also colloid particles of various sizes. Under these circumstances it is a "leaky" ultrafilter membrane and the fluid on both sides of the membrane will contain colloid. The first problem is to determine whether edema fluid is a pure ultrafiltrate containing salts and water in the same proportions as in the blood plasma but with very little or none of the proteins of the plasma. In order to determine this we have examined specimens of edema fluid (anasarca) from eight cases of nephritis and have found the total plasma proteins in this fluid to vary from 0.04

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per cent to 0.25 per cent (table 1). The mean value is 0.13 per cent. We have also examined the ascites of a dog made edematous within a period of

TABLE I

Examination of Edema Fluid in Nephritis and Nephrosis

Patient	% Protein in Edema Fluid	Edema Fluid		Plasma		Diagnosis
		Mg. % Na	Mg. % Cl	Mg. % Na	Mg. % Cl	
G. L.	.07%	333	452			Acute glomerulonephritis
H. N.	.04%					Subchronic glomerulonephritis with nephrotic element.
E. V.	.16%					Subchronic glomerulonephritis with nephrotic element.
E. V.	.25%					Subchronic glomerulonephritis with nephrotic element.
S.	.19%	340	408	335	393	Nephrosis
S.	.16%	326	398	338	387	Nephrosis
G. F. C.	.07%					Subacute glomerulonephritis
G. F. C.	.08%					Subacute glomerulonephritis

24 hours by reducing the plasma proteins in his blood and we have found the percentage of protein in this fluid to be 0.14 per cent. In five cases of chronic heart failure the amount of protein in edema fluid has varied from 0.1 per cent to 0.51 per cent, the mean value being 0.28 per cent (table 2).

TABLE II

Examination of Edema Fluid in Cardiac Failure

Patient	% Protein in Edema Fluid	Edema Fluid		Plasma		Diagnosis
		Mg. % Na	Mg. % Cl	Mg. % Na	Mg. % Cl	
C.	.27%	308	373	319	351	Congestive heart failure due to hypertension coronary disease.
G.	.23%	338	384	353	398	Congestive heart failure due to mitral disease.
B.	.51%	335	406	346	380	Congestive heart failure due to hypertension coronary disease.
E.	.29%	335	393	337	366	Congestive heart failure due to mitral disease.
H. W.	.1%					Congestive heart failure. Mitral stenosis.

These somewhat higher values in heart failure are probably explained by the fact that the increased capillary pressure which increases the tendency to filtration in heart failure is accompanied by a dilatation of the capillaries and stasis. Landis[1] has shown that stasis and dilatation can bring about some leakage of protein through a normal capillary ultrafilter. There is

also frequently a tendency to anoxemia in heart failure. Essex and Ort [2] have shown that anoxemia alters the permeability of the capillaries. Our values for edema fluid are in essential agreement with the protein concentrations in anasarca fluid found by Darrow, Hopper and Cary,[3] Leiter,[4] Shelburne and Egloff,[5] and Landis.[1] Beckmann [6] on the other hand has found higher concentration of protein in anasarca fluid but even the highest figures are less than many of the values found for lymph from a dog's leg by Drinker and Field [7, 8] and by Weech, Goettsch and Reeves.[9] We were very careful to avoid contamination with blood in collecting our specimens. The edema fluid was allowed to flow freely from the Southey tubes inserted into the subcutaneous tissues for at least a half hour before collecting in test tubes for chemical examination. It is reasonable to assume from our figures that the capillary is a fairly good ultrafilter during the process of formation of edema in nephritis but is probably a little more "leaky" in heart failure.

The Mechanism of Edema Formation

Starling [10] paved the way to an understanding of the mechanism of edema formation when he performed his perfusion experiments on dogs. His experiments proved definitely that the presence of colloid within the perfusion fluid decreased the tendency to edema. Edema occurred when only salts and water were used as perfusion liquid. Before the abnormal conditions may be discussed, it is necessary that one analyze the normal mechanism of fluid exchange in the tissues. We know from the work of Landis [11] that there is a gradual pressure fall along the capillary. Normally the average pressure at the arterial end of the capillary is 32 mm. Hg. At the venous end of the capillary, the pressure is about 12 mm. Hg and at the middle of the capillary loop about 22 mm. Hg. This, of course, is exactly what was predicted by Starling and Schade [12] in their early discussions of the subject, but until the work of Landis actual values for these pressures were unknown. This capillary pressure tends to force water and salt through the capillary wall and out into the tissue spaces. The colloidal osmotic pressure opposes this tendency for water and salt to leave the capillaries. From values we shall present later, it will be seen that the average colloidal osmotic pressure in man is 22 mm. Hg and therefore exactly equals the hydrostatic pressure within the capillary at the middle of the loop. It is therefore quite obvious that at the arterial end of the capillary, water and salt will be forced out of the vessel into the tissue spaces as long as the hydrostatic pressure is greater than the osmotic pressure. When these two pressures become equal, as they do in the middle of the capillary, fluid and salt will enter into the vessel as fast as they leave and no loss or gain will occur. At the venous end of the capillary, however, the osmotic pressure is higher than the hydrostatic pressure and therefore water and salts will stream into this half of the tube. Therefore in a normal capillary the amount of fluid

and salt forced out of the capillary at its arterial end will be approximately equalled by the amount of water and salt "pulled" into this tube at the venous end. We have modified Schade's original diagrams of fluid exchange in the capillary. Figure 1 represents the normal mechanism of fluid exchange along the capillary.

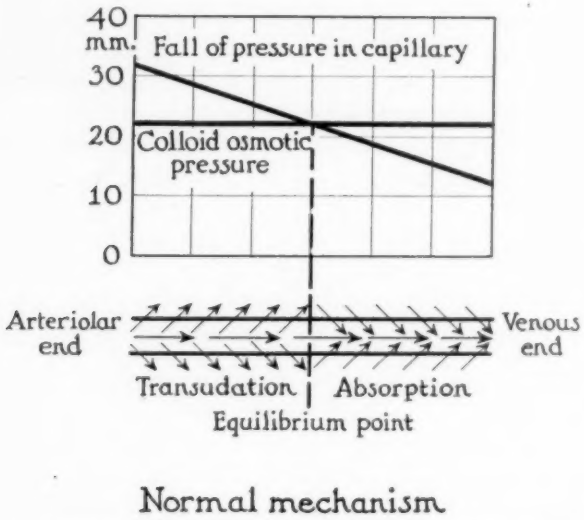
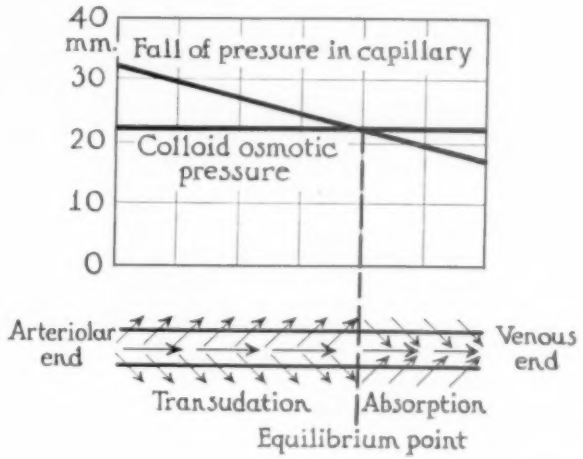


FIG. 1. Graphic presentation of fluid exchange in the capillaries.

Hydrostatic pressure and colloid osmotic pressure are not the only factors involved in edema formation. From this very simple discussion of normal fluid exchange in the capillaries, it appears obvious that the following factors might cause increased transudation and lead to edema formation: (1) increased hydrostatic or capillary pressure, (2) decreased plasma colloid osmotic pressure, (3) increased permeability of the capillaries, and (4) increased colloid osmotic pressure in the tissue surrounding the capillaries. Of these factors we believe that the increased hydrostatic pressure and the decreased osmotic pressure within the capillary are the most important. The hydrostatic pressure of edema fluid within the tissues themselves can not be wholly disregarded. In one case of edema due to heart failure we found this hydrostatic pressure to be approximately 8 cm. of water. This would decrease the active filtration pressure by just that much and thereby decrease the tendency to formation of further edema.

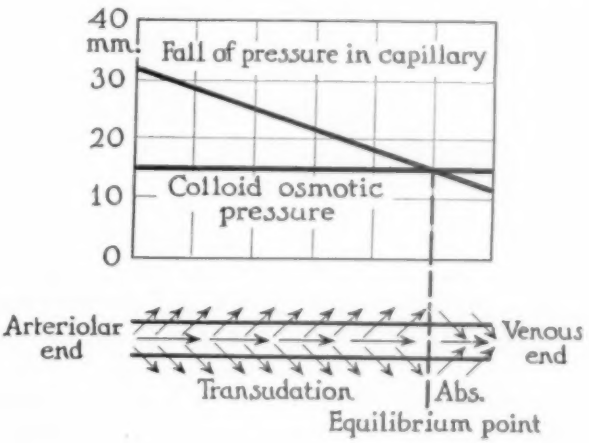
Let us now see what will happen if we vary some of the forces normally active in fluid exchange. If, for instance, we should increase the venous pressure, the point of balance between hydrostatic pressure within the capillary and osmotic pressure of the plasma colloids will shift towards the venous end of the capillaries. (Figure 2.) This will allow more fluid to pass out of the capillary since a greater proportion of the capillary will have a hydro-

static pressure higher than the osmotic pressure. If this process continues for any length of time it is obvious that edema must result. This is what happens when the right heart fails and the venous and capillary pressures rise in consequence of this heart failure. If instead of increasing the venous pressure we should decrease the colloid osmotic pressure (figure 3) and the



Mechanism with increased venous pressure (congestive heart failure)

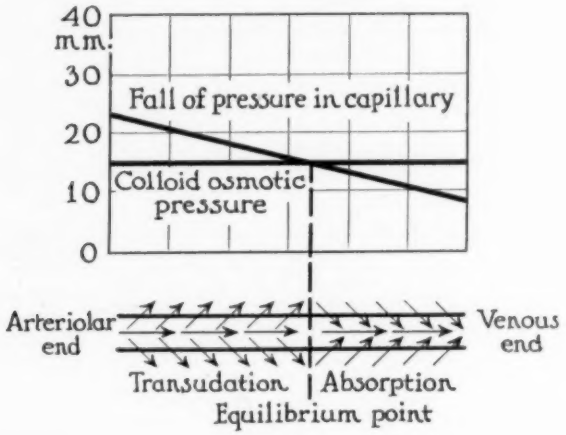
FIG. 2. Graphic presentation of fluid exchange in the capillaries.



Mechanism with reduced colloid osmotic pressure

FIG. 3. Graphic presentation of fluid exchange in the capillaries.

capillary pressure remains the same, the equilibrium point will again shift to the venous end of the capillary and more of the capillary will be given over to transudation and less to absorption. This also would lead to edema formation. In our opinion this is exactly what happens in nephrosis and nephritis * with edema. At this point it might be well to consider that the body might accommodate itself to this lowered colloid osmotic pressure by reducing capillary pressure. If such should occur, a state might be reached much as is diagrammatically represented in figure 4. It is possible that this



Possible compensatory vascular mechanism with reduced colloid osmotic pressure

FIG. 4. Graphic presentation of fluid exchange in the capillaries.

mechanism is at times called upon for we shall see that certain reductions in colloid osmotic pressures can occur without edema. Below a certain value edema will practically always result because the body can not accommodate itself to these very low colloid osmotic pressures.

Up to the present we have not taken into consideration the possibility that there could be an increased permeability of the capillaries. In our discussion of the capillary wall as an ultrafilter we have stated that very little protein leaks through, so that if the capillary has become more permeable, it apparently has become more permeable only to salts and water. Such a permeability would not alter the mechanism of edema formation unless a change in permeability would occur only in one end of the capillary and not the other. If we assume, and it appears logical to do so, that the changes in permeability must of necessity occur throughout the whole capillary, then any such change would make no difference in the amount of edema. It

* In acute and chronic nephritis heart failure is often present also and the increased capillary pressure is an added factor in edema formation.

is obvious that if more fluid is forced out of the capillary in the arteriolar end, more fluid will also be re-absorbed into the capillary at the venous end, so that although more fluid may pass through the capillary wall in both ways, the end result is the same.

If the capillary wall loses its property of holding back colloid particles then there will be a colloid osmotic pressure developed by the protein particles in the filtrate on the outside of this " leaky " capillary. This colloid osmotic pressure of the proteins in the filtrate surrounding the " leaky " capillary will tend to increase the filtration rate across the wall at the arterial end of the capillary and to decrease the absorption of fluid at the venous end. In other words the " leaky " ultrafilter tends to reduce the effectiveness of the osmotic pressure of the proteins within the capillary by exactly the amount of colloid osmotic pressure present in the ultrafiltrate on the outside. Calculations of the actual colloid osmotic pressure of concentrations of serum proteins of the order of those found in edema fluids show them to be negligible as factors in edema formation.

The Measurement of Colloid Osmotic Pressure

Starling [10] was the first to measure the osmotic pressure of the plasma colloids. He obtained a value of 30 to 41 mm. Hg for the normal osmotic pressure of the plasma colloids. From values of the capillary pressure given by Landis,[11] we know that these original measurements were far too high. This can be accounted for by his method which was to take concentrated serum, determine the colloid osmotic pressure and calculate the normal osmotic pressure on the basis of a straight line relationship between concentration and pressure, thereby disregarding the very large relative volume of the colloid particles or the " b " factor of the Van der Walls equation for the relation between pressure and volume of a gas. Other errors also crept into his method, such as inconstancy of temperature and the long time necessary for completion of the experiment which allowed changes to occur in the protein micel. Later Verney [13] in Starling's laboratory used a modification of the Starling method and obtained values from 22.8 to 25 mm. Hg. Krogh [14] in 1929 obtained a value of 27.9 mm. Hg. Govaerts [15] in 1924 found pressures of 25.7 to 29.4 mm. Hg in the normal and in cases of nephritis with edema 8.8 to 9.6 mm. Hg. Landis [16] in 1930 using a method similar to Starling's obtained a value of 18.3 mm. Hg for normal osmotic pressure. Kylin [17] in 1929 obtained a value of 30 mm. Hg and Muntwyler, Way, Binns and Myers [18] in 1933 found the normal osmotic pressure to be from 21.7 to 25.2 mm. Hg. After Sørensen [19] had laid the foundation for the dynamic determination of the colloid osmotic pressure, Schade [12] saw the advantages in this method and perfected a microtechnic. We have used the Schade method in all our determinations. This does away with all the disadvantages of the Starling method in that the temperature is kept constant so that the osmometer will not act as a thermometer. The plasma is used

in its normal concentration and the entire experiment requires only 2 to 4 hours. We have been able to demonstrate with our method that the above mentioned factors can cause great differences in the pressure readings. For example, using our method a sudden change in temperature of 0.1 of a degree C. can give errors of the order of 25 per cent. We have also determined that allowing sterile plasma to stand at room temperature for 48 hours may increase the osmotic pressure as much as 19 per cent. Since in this method we are actually performing ultrafiltration and not measuring the osmotic pressure of the plasma against water or any other solution, there will be no difference in ionic concentration on the two sides of the membrane other than that brought about in accordance with the Donnan equilibrium. We are therefore actually measuring the colloid osmotic pressure as it affects ultrafiltration in the human capillaries or in other words the "effective" colloid osmotic pressure.

Normal Colloid Osmotic Pressure of the Blood Plasma in Man

We [20] have examined colloid osmotic pressure in 22 normal persons and have found the mean pressure to be 21.4 mm. Hg at 37° C. (table 3). The experimental error of our procedure showed a standard deviation of the

Table III

Normal Colloid Osmotic Pressure Values in Man

Case	Albumin	Globulin	Fibrinogen	Total Prot.	Osmotic Pressure mm. Hg at 37° C.
W. S.					19.8
W. C.					19.7
E. C.					20.6
E. G.					20.2
R. H.					25.1
V. A.					18.4
W. H.					22.6
E. B.					22.6
B.					19.9
O. F.					23.1
G. K.					20.9
A. F.					17.9
K. S.					20.0
G. J.					19.4
L.					25.2
B.					25.6
P. J.					17.0
A. M.	3.85%	1.86%	.70%	6.41%	23.7
H.	4.49%	2.00%	.41%	6.9%	22.3
H.	4.49%	1.96%	.36%	6.81%	20.8
S.	4.39%	2.18%	.67%	7.24%	23.1
S.	4.03%	2.00%	.64%	6.67%	20.5

Mean Pressure 21.4

Standard deviation 2.5

These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant.

mean of 0.6 mm. Hg or a probable error of the mean of 0.4 mm. Hg. The biological scatter is measured by a standard deviation of $\pm$ 2.5 mm. Hg. The values ranged from the lowest value of 17 mm. Hg to the highest value of 25.3 mm. Hg. Our mean agrees very well with the mean value for pressure in the middle of the human capillary as determined by Landis' measurements. Values very much higher than these would lead to an absorption of the body fluids into the blood vascular system, their excretion through the kidneys, and a consequent dehydration of the body. Values much lower than these would lead to generalized edema formation. We believe that our mean is very close to the actual value. Our values are in essential agreement with those obtained by Schade,[12] Verney,[13] Landis,[16] and Muntwyler, Way, Binns and Myers [18] and are much lower than those obtained by Starling,[10] Krogh,[14] Govaerts [15] and Kylin.[17]

We have determined the colloid osmotic pressure of normal dogs and have found it to average 18.5 mm. Hg. The highest value was 21.7 and the lowest value 17.2 mm. Hg (table 4).

TABLE IV

Colloid Osmotic Pressure Values in Normal Dogs

Date	Albumin	Globulin	Fibrinogen	Total Protein	Osmotic Pressure mm. Hg at 37° C.
2/3/31					21.7
8/17/31	3.49%	2.69%	.41%	6.59%	18.0
9/15/31	4.81%	2.47%	.43%	7.71%	17.9
9/18/31	4.56%	2.23%	.65%	7.44%	18.8
9/19/31	4.90%	1.77%	.58%	7.25%	19.6
9/30/31	3.61%	1.24%	.45%	5.30%	17.3
10/6/31	3.8%	1.69%	.44%	5.93%	17.2
10/26/31	4.67%	1.6%	.49%	6.76%	21.2

Mean pressure 18.5 mm. Hg

(These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant.)

COLLOID OSMOTIC PRESSURE OF THE BLOOD PLASMA IN CASES OF NEPHROSIS AND NEPHRITIS

We [21] have made 24 determinations of the colloid osmotic pressure in 14 cases of nephritis with edema (table 5). Whenever edema was present, the colloid osmotic pressure was always lower than 15 mm. Hg; when the colloid osmotic pressure was 16 mm. Hg or more, edema was absent or was being absorbed. The average colloid osmotic pressure for these edematous cases was 8 mm. Hg. This value agrees well with the values obtained by Goevarts,[15] Schade,[12] Fahr and Swanson,[22] Muntwyler, Way, Binns and Myers [18] and Kylin.[17] The colloid osmotic pressure of one case of chronic nephritis in uremia without edema was found to be 27 mm. Hg. This patient, however, had hypertension and we have found that in hypertension

the osmotic pressure of the plasma proteins tends to be slightly higher than normal.

TABLE V

Colloid Osmotic Pressure in Cases of Nephritis with Edema

Date	Name	Albumin	Globulin	Fibrinogen	Total Prot.	Osmotic Pressure mm. Hg at 37° C.	Edema
6/9/30	S. M.	.95%?			3.69%	6.2	4+
6/13/30	S. M.					8.8	4+
6/18/30	S. M.					6.4	4+
6/23/30	S. M.					10.1	4+
8/11/30	S. M.					8.6	4+
9/29/30	D. G.					9.2	4+
4/14/31	D. G.					9.4	4+
8/11/31	D. G.	2.14%	1.76%	.65%	4.55%	10.6	4+
10/10/31	D. G.	2.39%	2.19%	.72%	5.29%	12.6	4+
10/30/30	B. C.					10.8	3+
7/18/30	F. H.					8.5	4+
10/1/30	F. H.					9.4	4+
10/7/30	E. W.					9.6	4+
10/22/30	O. M.					10.2	4+
8/7/31	M. W.	1.14%	1.63%	.47%	3.25%	7.6	4+
12/27/32	E. J.					8.1	4+
2/8/32	E. J.					6.6	4+
1/2/33	M. A. B.					8.1	4+
8/3/33	I. C.	2.38%	1.84%	.65%	4.87%	8.8	4+
6/28/33	D. P.	1.28%	1.51%	.40%	3.19%	6.6	4+
6/29/33	H. N.	1.08%	1.19%	.68%	2.95%	7	4+
6/21/33	E. V.					10.6	4+
3/20/35	G. L.	2.51%	1.73%	.61%	4.85%	10.3	3+

(These values are not corrected for the error due to the addition of sodium oxalate as the anti-coagulant.)

THE EFFECT OF GUM ACACIA INJECTIONS ON NEPHROTIC EDEMA IN MAN

In order to demonstrate that the edema in nephrosis and nephritis was due merely to a reduced colloidal osmotic pressure in the plasma, we searched for some inert colloid which could be injected into the blood stream and which would have no other effect than to raise the colloid osmotic pressure. Hartmann [23] had shown that the intravenous injection of 30 per cent gum acacia in nephrotic patients led to a diuresis. Thirty per cent gum acacia solution has a colloid osmotic pressure many times higher than that of normal plasma. In fact, a 6 per cent gum acacia solution has approximately the same colloid osmotic pressure as normal plasma. Therefore it should be possible by injecting sufficient amounts of 30 per cent gum acacia to raise the colloid osmotic pressure to a point where edema would be absorbed. Referring back to our scheme of a capillary if we raise the colloid osmotic pressure sufficiently we should move the equilibrium point near the middle of the capillary and therefore have less transudation and more absorption. We have injected this solution into six patients with nephritis or nephrosis. In only three of these cases was it possible to inject enough gum acacia to produce the desired effect. However, when sufficient gum acacia could be

TABLE VI

The Effect of the Injection of Gum Acacia in a Case of Subacute Glomerulonephritis with Edema

Date	Weight	C.c. of 30% Gum Acacia	Intake	Output	Fluid Gain + or Loss −	NaCl in Urine		Colloid Osmotic Pressure	Acacia in 24 Hrs. Urine
						%	Gm./24 Hrs.		
1/25/33	171		400 c.c.	340 c.c.	60 c.c.+			on 1/2/33 = 8 mm. Hg	
1/26/33			400 c.c.	550 c.c.	150 c.c.−				
1/27/33			400 c.c.	500 c.c.	100 c.c.−				
1/28/33		300 c.c.	615 c.c.	1875 c.c.	1260 c.c.−				
1/29/33		400 c.c.	750 c.c.	1950 c.c.	1250 c.c.−	.62	9.55		7.38 Gm.
1/30/33		300 c.c.	675 c.c.	2100 c.c.	1425 c.c.−	.64	11.98	Before acacia 12 mm. Hg / 1 hr. after acacia 15 mm. Hg	7.6 Gm.
1/31/33			400 c.c.	2750 c.c.	2350 c.c.−	.55	13.8		4.5 Gm.
2/1/33	134		400 c.c.	2725 c.c.	2325 c.c.−	.64	17.4	13 mm. Hg	2.5 Gm.
2/2/33	134		310 c.c.	1400 c.c.	1090 c.c.−	.65	8.8		.69 Gm.
2/3/33			400 c.c.	1300 c.c.	900 c.c.−	.47	5.85	12.6 mm. Hg	
2/4/33			495 c.c.	1150 c.c.	655 c.c.−	.61	5.74		.93 Gm.
2/5/33	126		450 c.c.	650 c.c.	200 c.c.−	.64	4.1		

injected without severe reactions marked diuresis followed. We shall give the results of only one of these experiments performed in a case of subacute glomerulonephritis with very marked edema (table 6). The colloid osmotic pressure was 8 mm. Hg and the patient on an intake of 400 c.c. a day was barely maintaining her fluid balance. She was neither gaining nor losing edema. On the first day of the experiment she was given intravenously 300 c.c. of 30 per cent salt-free gum acacia furnished by the Eli Lilly Co. This day with an intake of 600 c.c. her output rose to 1900 c.c., a loss of approximately 1300 c.c. of body fluid. The next day she was given 400 c.c. of gum acacia and again lost approximately 1300 c.c. of fluid. The third day she was given 300 c.c. gum acacia and lost approximately 1400 c.c. more fluid than she took in. On this third day the osmotic pressure of the plasma colloids was 12 mm. Hg before the last injection of gum acacia, while after the injection the osmotic pressure was 15 mm. Hg.* Several days later the osmotic pressure was still 13 mm. Hg. The patient continued to put out large amounts of fluid. In a period of seven days she lost 11 liters of edema fluid with a corresponding loss in weight. The mere addition of an indifferent colloid to the blood plasma increased the total colloid osmotic pressure to a point at which fluid was drawn into the blood, carried to the kidneys and excreted as urine, thus producing a marked diuresis. During the time of this very marked diuresis of water there was also a very marked increase in the output of salt. At the height of the diuresis, the patient put out 17.4 gm. of salt in one day on an intake of 2.5 gm. of salt. In other words, this patient was putting out urine which contained nearly the same amount of salt as is present in normal tissue fluid. This tends to prove that the kidney is able to excrete salt very readily in nephrosis or nephritis with edema if the colloid osmotic pressure is raised sufficiently so that tissue fluid can be absorbed. These experiments also prove that the increase of the colloid osmotic pressure by some inert colloid not normally found in the blood is sufficient to cause an absorption of the edema with consequent excretion of water. The kidney itself has no difficulty in excreting water and salt if water and salt can be absorbed from the tissue spaces.

Conclusions

1. The edema fluid in nephritis, nephrosis and cardiac failure is a nearly pure ultrafiltrate of the blood plasma.

2. The formation of edema is for the most part a result of imbalance between the forces of capillary hydrostatic pressure and colloid osmotic pressure of the plasma. A substantial increase in capillary pressure or decrease in colloid osmotic pressure or a combination of both results in edema formation.

3. The method of Schade for the determination of the "onkotic" pres-

* Immediately after injecting gum acacia fluid is drawn into the blood, the plasma volume is increased and the colloids are diluted. Therefore the calculated colloid osmotic pressure is never attained.

sure is the logical method for the determination of the "effective" colloid osmotic pressure of the plasma because it measures the hydrostatic pressure at which ultrafiltration of the plasma salt and water just equals the reabsorption. For this reason in using this method it is unnecessary to calculate or measure the Donnan effect. The thermostatic control of temperature rules out any sudden thermometric effect during the measurement.

4. The normal colloid osmotic pressure of the plasma in man is approximately 21.4 $\pm$ 2.5 mm. Hg.

5. The normal colloid osmotic pressure of the plasma in dogs is 18.5 mm. Hg.

6. In nephrosis and nephritis with edema the colloid osmotic pressure is usually lower than 15 mm. Hg and averages 8 mm. Hg.

7. The injection of concentrated solutions of an inert colloid (gum acacia) increases the colloid osmotic pressure of the plasma and causes a disappearance of the edema with a corresponding diuresis of water and salt in the same proportions as they are found in edema fluid.

8. Retention of salt in nephritis is not due to renal insufficiency but is consequent to prerenal deviation in the ultrafiltrate or edema fluid.

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CUTANEOUS MANIFESTATIONS IN PSYCHOTIC AND PSYCHONEUROTIC INDIVIDUALS *

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IT is known that, as a result of their disorder, a small percentage of individuals with nervous or mental abnormalities develop habits which result in skin lesions, or even may become victims of constantly self-inflicted injuries to the skin or mucous membranes. These are cases of true dermatitis factitia. Some of these acts may be the result of a desire for attracting sympathy or attention to the individual, as in one of the cases mentioned recently by Klauder [1] in which a hysterical woman systematically and secretly used lysol to produce extensive wheals or bands on her arms, which were exhibited to her acquaintances for their commiseration. Such cases are, however, merely behavior problems; although a mental or nervous disorder is responsible for the abnormal habit, it is not directly causative of the cutaneous lesion.

There appears to be a certain amount of evidence that in various psychoses, psychoneuroses and neuroses, in some types more than in others, there is a tendency to the development of more or less definite types of skin diseases; that is to say that, whatever may be the mode in which the effect is produced, these mental and nervous disorders are etiologic factors in the production of certain types of skin lesions.

The literature dealing with this subject is not voluminous, and, especially as regards the psychoses and psychoneuroses, is indefinite and lacking in clinical precision. I have, therefore, thought that it would be of interest to set down my personal clinical findings in the observation of a very considerable number of psychotic and psychoneurotic patients, in a definite percentage of whom skin lesions were observed, without there being, so far as could be observed, any other etiologic factor than the psychogenic one; further, to classify as far as possible the types of cutaneous lesions associated with definite psychogenic states and finally, to give the therapeutic result following a particular mode of treatment.

The data, which I have tried to make as complete as possible in regard to the clinical aspects, may, I hope, induce others, who have the opportunity, to make similar observations, with a view of verifying whether it is merely a conjecture or an established fact that psychogenic disorders are definite etiologic factors in cutaneous disorders; also, perhaps, to discover the mode of causation.

Theoretically, there are different ways in which nervous and mental disorders may affect the skin, especially its trophism. Of these perhaps

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the most likely are the increased excitability and emotionality, acting probably on either or both the endocrine or other body secretions or the autonomic nervous system, particularly the trophic or sensory nerves supplying the nutrient vessels. Such factors are known to affect the skin in normal as well as in neurotic and psychotic subjects; but in psychotics especially the abnormal emotionality should be a particularly strong factor in producing effects upon the skin, although we are much in the dark in regard to the exact mechanism of such production.

A brief résumé of the available literature will be in order before citing my personal contribution. It will be noted that the authors quoted give more attention to the effects of emotionality upon the skin in normal sane subjects than in psychotics or psychoneurotics.

Eller [2] was one of the first in this country, in 1929, to write on the subject of nervous and mental factors affecting the skin. He mentions as a recognized fact that the blood vessel tonus is regulated by several factors, among which may be included the psyche acting through the visceral nervous system, either the parasympathetic or sympathetic. These in turn may be influenced by the internal secretions. This vascular influence, of course, occurs in the skin as well as in other organs.

According to Eller, the skin conditions occurring in this group are: (1) dermatitis factitia; (2) the compulsion neuroses, namely, dermato-thalassia, etc.; (3) dermato-phobias; (4) emotional urticaria; (5) hysterical pemphigus, which is said to exist; (6) alopecia areata, lichen planus and certain eczemas of psychogenic origin.

Eller cited Strandberg who observed the frequent occurrence of vasomotor and trophic disturbances of the skin in insane persons, among which he included acrocyanosis, abnormal hair growth, anomalies of sweat secretion, trophic and other disturbances of the nails, etc., especially in patients with dementia praecox.

Bonjour,[3] writing in 1929 upon the influence of the mind on the skin, cites Sack (of Baden-Baden) who expressed the belief that in certain psychogenetic phenomena the skin could be used as an organ of expression, especially if it had some pathologic disposition to act thus. Bonjour himself thought that warts, eczema and urticaria could be therapeutically influenced by suggestion; patients showing such lesions were persons whose nervous systems were affected either through emotions or through some other cause of excitement.

Joltrain [4] states that " Emotional shock is always followed by a humoral disequilibrium—a hemoclastic crisis which is always followed by a series of phenomena. Herpes, dermatographism, etc. appear after strong emotions in those having such a disposition. Emotion can be considered as an antigen, as something which in a hypersensitive organism frees sensitizing substances."

Horan [5] insists that the emotions acting through the endocrines and cir-

culatory systems can and do bring about many pathologic conditions of the skin.

Stokes [6] of Philadelphia, writing in 1932, says: "I have reached the belief that it is often impossible really to comprehend the urticarias of adult life, which are of more than two weeks' duration, without a genuine study of the personality problems involved." In an article published in 1930 Stokes and Pillsbury [7] stated: "The larger our experience, the more careful our search, the more we are inclined to believe that in the urticarias and urticarial dermatitides of middle life, in the diathetic eczemas and rosacea, and even in dermatoses, which, like epidermatophytoses, seem far removed from psychologic considerations, the tension make-up, the personality defect, the conflict and anxiety, the repression and complex, have their place as causal influences." These writers considered that the mode in which the psychologic factor acts to produce urticaria was that emotion predisposed to acidity, acidity favored production of the gas bacillus, and the gas bacillus caused production of histamine and wheals on the skin.

Crutchfield,[8] writing in 1932 upon the emotional and psychic factors in skin disease, classes these types of skin lesions in four groups:

1. Those in which there is some definite organic pathologic lesion in the sensory or trophic nerve;
2. Those conditions which are a result of pathologic changes in the peripheral nerves (trophic ulcers, gangrene);
3. Those conditions in which no known pathologic lesions exist in the nervous system but in which skin lesions are pronounced:
4. Disturbances in the autonomic nervous system. This is the group in which emotions play the most important part.

There is a less definite class composed of skin diseases which cannot be placed in any anatomic group but which are produced by the emotions of the patient. These may be aggravated, prolonged or become incurable due entirely to the mental reactions of the patients.

Klauder [1] has just published an article on the psychogenic aspects of skin diseases. He gives a long list of such lesions which, besides those of a circulatory or sensory nerve origin, includes stigmata, trichotillomania, angiospasm, etc. He mentions anesthetic areas observed in hysterical patients; also, that psychoneurotics have a peculiar lability of the vasomotor apparatus manifested in disorders of the peripheral circulation. Peripheral circulatory disturbances in psychopathy are stressed. Klauder thinks that dermatographism of psychoneurotics is closely related with angioneurotic edema, urticaria and frank dermatitis or acute eczema. Further, that cutaneous phenomena, characterized by vascular dilatation, erythema and exudation, when appearing and disappearing suddenly are suggestive of psychic or allergic causation.

My personal observations refer to skin lesions noted in psychotic and psychoneurotic individuals for which no other etiologic factors could be

found apart from the nervous or mental disturbance. A total of 1350 such patients was observed. The average age was 44 years; the minimum, 38 years. Of this total group, 150 patients were classed as psychoneurotics, and of these 27 (18 per cent) showed or developed skin lesions during the period of treatment; 1200 patients were classed as psychotics and, in these, 76 cases (6.33 per cent) of skin diseases were observed or developed during the period of treatment.

TABLE I

Percentage of Skin Diseases in Sub-Groups of Psychoneuroses

150 Cases (11% of total patients observed)

Sub-group	No. Cases Skin Lesion Observed	Percentage of Psychoneurosis Group
Hysterical	14	9⅓%
Anxiety state	9	6%
Psychasthenia	4	2⅔%
TOTAL	27	18%

Table 1 gives the percentage of each psychopathologic sub-group for the psychoneurotic cases and the total percentage of skin lesion cases observed in each sub-group.

TABLE II

Types of Skin Diseases Accompanying Psychoneuroses

TYPE	SUB-TYPE	No. of patients in group	TYPE OF SKIN DISEASES	No. in group under treatment	Recovered	Improved	Unchanged	REMARKS
PSYCHONEUROSIS	HYSTERICAL TYPE	14	Acne vulgaris	8	2*	1	5	*Skin lesions cleared up and remained symptom free for over nine months.
			Herpes zoster	4	0	3*	1	*Suffered a relapse whenever treatment was discontinued.
			Seborrheic dermatitis	2	0	1*	1	*Improved also in general health—mentally and physically.
	ANXIETY STATE	9	Acne vulgaris	5	2	1	2	This entire group improved in general health
			Eczemas of undetermined origin	3	0	1	2	
			Dermatitis factitia	1	0	1	0	
	PSYCHASTHENIA	4	Impetigo	2	0	1	1	
			Seborrheic dermatitis	1	0	1	0	
			Urticaria	1	1*	0	0	*Skin lesions cleared up after 2½ months of treatment.

"Recovered" as here used indicates that the manifestation did not recur for a period of three months.

Table 2 gives the types of skin lesions observed in the foregoing psychoneurotic sub-groups with the result of treatment.

TABLE III

Percentage of Skin Disease in Sub-Groups of Psychoses

PSYCHOSIS

1200 Cases or 89% of Total Patients Observed

Sub-group	No. Cases Skin Lesion Observed	Percentage of Psychosis Group
Dementia praecox	49	4 %
Manic depressive	16	1¼ %
Psychopathic personality	6	½ %
Psychosis with mental deficiency	3	¼ %
Miscellaneous undiagnosed psychosis	2	⅙ %
TOTAL	76	6⅓ %

Table 3 gives the percentage of each psycho-pathologic sub-group in the 1200 psychotic cases and the percentage of skin lesions observed in each sub-group.

TABLE IV

Types of Skin Diseases Accompanying Psychoses

TYPE	SUB-TYPE	No. of patients in group	TYPE OF SKIN DISEASE	No. in group under treatment	Recovered	Improved	Unchanged	REMARKS
DEMENTIA PRAECOX	SIMPLE	8	Acne vulgaris	4	1	2	1	
			Follicular eruption of the trunk and extremities	2	1	0	1	
			Herpes zoster	1	0	1	0	
			Psoriasis with infiltrated patches	1	0	1	0	
	HEBEPHRENIC	20	Eczemas of undetermined origin	8	0	3*	5	*Edematous lesions cleared up quite unexpectedly only during treatment.
			Herpes zoster	2	0	1	1	
			Ichthyosis	2	0	2	0	
			Seborrheic dermatitis	6	1	2	3	
			Pellagra	1	1*	0	0	*Dietary restrictions were observed in addition to treatments.
			Pruritus	1	0	1	0	
	PARANOID	10	Acne vulgaris	6	2	1	3	
			Seborrheic dermatitis	3	1	1	1	
			Eczemas of undetermined origin	1	0	0	1	
	CATATONIC	11	Psoriasis	2	0	1	1	
			Ichthyosis	2	0	0	2	
			Seborrheic dermatitis	6	0	1	5	
			Eczemas	1	0	0	1	

TABLE IV—*Continued*

Type	Sub-type	No. of patients in group	Type of Skin Disease	No. in group under treatment	Recovered	Improved	Unchanged	Remarks
Manic Depressive	Manic	6	Urticaria	5	0	1	4	
			Seborrheic dermatitis	1	0	1	0	
	De-pressed	8	Acne vulgaris	5	1	2	2	
			Herpes zoster	1	0	1	0	
			Psoriasis with infiltrated patches	1	0	1	0	
			Eczema	1	0	1	0	
	Involl. Melancholy	2	Urticaria	2	0	2	0	Improved in general mental and physical condition while on treatment.
	Psychopathic Personality	6	Dermatitis factitia	3	0	2	1	
			Herpes zoster	2	0	1	1	
			Acne vulgaris	1	1	0	0	
	Psychosis with Mental Deficiency	3	Seborrheic dermatitis	2	0	1	1	
			Fungus infection of scalp	1	0	1	0	
	Misc. Undiagnosed Psychosis	2	Ichthyosis hystrix	1	0	1	0	Clinical improvement in metabolism and gastrointestinal functions, also mentally.
			Eczema of undetermined origin	1	0	1	0	

"Recovered" as here used indicates that the manifestation did not recur for a period of three months.

Table 4 gives the types of skin lesions observed in the psychopathic sub-groups with the psychotic sub-groups, and the result of treatment.

Table 5 gives a comparison of the results of treatments of skin lesions in the two main groups.

TABLE V

Comparative Response to Treatment of Skin Diseases in Psychoneurotic and Psychotic Cases
Total Number of Cases Observed = 1350

Psychoneurosis 150 Cases = 11% of Total	Cases in which skin lesions developed: 27 Cases or 18% of Group	Recovered = Five or 18%	
		Improved = Ten or 37%	
		Unchanged = Twelve or 44%	
	Cases in which skin lesions were not observed: 123 Cases or 82% of Group		
Psychosis 1200 Cases = 89% of Total	Cases in which skin lesions developed: 76 Cases or 6⅓% of Group	Recovered = Nine or 11⅘%	
		Improved = Thirty-two or 42%	
		Unchanged = Thirty-five or 46%	
	Cases in which skin lesions were not observed: 1124 Cases or 93⅔% of Group		

The skin lesions which were observed in the two groups were as follows:

Acne vulgaris
Dermatitis factitia
Pellagra with characteristic facies, pigmentation and exfoliation
Parapsoriasis lichenoides
Psoriasis with deeply infiltrated patches
Ichthyosis hystrix
Herpes zoster
Dermatophobias
Seborrheic dermatitis
Pruritus
Eczemas of undetermined origin

Studies of urine, blood, and basal metabolic rate were made routinely. The urine showed no significant departure from normal. Blood cholesterol was within normal limits in most of the patients. The fasting blood sugar was normal. The basal metabolic rate varied between minus 24 and plus 20. In this group of cases the schizophrenics had the lowest basal metabolic rate. None of these patients, regardless of the metabolic rate, showed any signs of disturbed thyroid function.

Roentgen-rays of the pituitary region showed normal size of the sella turcica without erosion in practically all the cases so studied. One case showed an abnormally large sella but without evidence of erosion.

Treatment of these psychotic and psychoneurotic patients with skin lesions consisted of the administration of U.S.P. standardized thyroid in tablets, in doses from ¼ to 3 grains per day, and of injections of ½ c.c. of antuitrin every other day. The dosages were varied to some extent according to the level of the basal metabolic rate, the pulse, weight, skin lesions and the degree of mental disturbances.

The response to this treatment was more favorable in psychoneurotic than in the psychotic group (table 5). In cases in which improvement took place the change was noted after three or four months of treatment (tables 2 to 4).

The use of this form of therapy was largely empirical. It was suggested by the frequency of endocrine disturbances associated with psychosis or psychoneurosis. The results obtained are not considered decisive.

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AN ANALYSIS OF 62 CASES OF PRIMARY CARCINOMA OF THE LIVER BASED ON 24,400 NECROPSIES AT BELLEVUE HOSPITAL *

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The material for this study of primary carcinoma of the liver was derived from 24,400 consecutive autopsies performed at Bellevue Hospital from 1906 to 1936. In selecting these 62 cases a review of all cases included in our protocols as primary carcinomata of the liver was carried out. Those cases which, either on analysis of the protocols, or, microscopically, did not represent typical examples of carcinoma, were excluded, together with those in which clinical records or microscopic preparations were not available. All cases were likewise excluded in which duct cell carcinoma of the pancreas was suspected, microscopically or otherwise.

In this presentation the classification and diagnostic criteria layed down by Eggel [1] are adhered to. Those cases with invasion or destruction, or with metastases, or with neoplastic thrombus formation, visible either grossly or microscopically, or both, are termed carcinoma.

Macroscopically three groups are considered:

1. The nodular form, in which the neoplasmic growth is represented by discrete nodules, varying in size from a few millimeters to several centimeters. These nodules may involve one or more lobes.
2. The massive form, in which there is one massive nodule occupying an entire lobe, usually the right. There may be numerous smaller tumor nodules in adjacent liver tissue. This form frequently merges with that of group 1.
3. A diffuse form in which it is impracticable to differentiate carcinoma from cirrhosis of the liver, except microscopically.

Microscopically, the differentiation between the primary liver cell and bile duct types is considered. Cases occur in which a differential diagnosis is difficult or impossible to make because of varying pictures in different parts of the tumor growth. These are included under a separate heading, namely, indeterminate or dual origin. According to this microscopic classification, 39 of the Bellevue Hospital cases are of liver cell type, 21 of bile duct type, and 2 of indeterminate or dual origin. These figures are presented at this point in anticipation of further analysis which depends on this division.

No individual survey has heretofore been made of so large a group. Hale-White [2] analyzed 25 cases occurring in 18,500 necropsies, an incidence of 0.13 per cent. McIndoe and Counseller [3] analyzed 62 cases collected from 42,276 necropsies, an incidence of 0.14 per cent. The limits of varia-

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tion of incidence extend from 0.08 per cent by McIndoe and Counseller in their own cases, to 0.33 per cent by Von Glahn and Lamb [4] and Fried.[5] In the present analysis the incidence was found to be 0.25 per cent, or one case of primary carcinoma of the liver in every 394 necropsies.

The sex incidence in the 62 cases at Bellevue Hospital was 53 males and 9 females. However, accurate figures on the number of necropsies in males and females were not obtainable, the approximate ratio being three males to one female, thus giving a corrected incidence of 18 males to 9 females. Eight of the nine cases in females were in the bile-duct group and one in the liver cell group. The significance of this is not clear. Are the possible underlying etiological factors of significance? Does the predominance of cirrhosis of the liver in males play a rôle? No definite answer to these questions is available as yet.

In the Bellevue Hospital series 53 cases occurred in the white race, 4 in negroes, and 5 in the yellow race (4 Chinese and 1 Japanese). These latter figures comprise 6.4 per cent and 8.1 per cent, respectively, of the present series.

The incidence in negroes parallels the admission rate of that race to Bellevue Hospital. That of the yellow race, however, is much higher than the admission rate. Strong and Pitts [6] of Vancouver, where the Chinese populace is relatively larger than that of New York City, reported a higher incidence of primary carcinoma of the liver in the yellow race. They reported nine cases of primary carcinoma of the liver occurring in 1024 necropsies. Of the 9 cases eight were in Chinese. The number of necropsies on Chinese in their series was 115, making an incidence of 6.9 per cent in Chinese as compared with 1 case in 909 necropsies in white people, or an incidence of 0.11 per cent.

The yearly percentage incidence in the autopsy series of primary carcinoma of the liver including both liver cell and bile duct origin has shown great variation over the course of years from which this series is taken. No definite trend towards an increasing or decreasing incidence is determinable from our figures.

The average age incidence in the Bellevue Hospital series was 52.5 years —that of the liver cell type 51.2 years, and that of the bile duct type 54.8 years; no cases occurred in children. Classed according to decades the highest incidence is in the fifth, sixth and seventh decades, as shown in the following table.

TABLE I

Age Incidence	Liver Cell	Bile Duct	Dual Origin
30–39	3	3	
40–49	12	6	
50–59	14	4	
60–69	8	7	2
70–79	1	0	
80–89	1	1	

Analysis of Clinical History and Physical Findings

Clinically, it is impossible to distribute these cases into their respective anatomical groups. An attempt has been made to classify them clinically into one of the following six groups:

1. Those cases presenting chiefly history and symptomatology of cirrhosis of the liver. This group comprises the largest number: (18).
2. Those cases presenting chiefly history and symptomatology of disorders of biliary or gastrointestinal tracts. This group comprises the second largest group: (14).
3. The third group comprises those cases which present signs of a malignant growth at some site in the body characterized, clinically, by loss of weight, weakness, appearance of metastatic nodules elsewhere, etc. In this group are 14 cases, four of which were diagnosed clinically as primary carcinoma of the liver.
4. Those patients who enter the hospital on the surgical services and die before or shortly after intervention due to spontaneous hemorrhage from a ruptured carcinomatous nodule of the liver. There are three cases in this group.
5. Those patients whose symptoms and signs do not point to pathological changes in the liver. There are six cases in this group.
6. Those patients dying before any diagnosis is possible. In this group are seven cases.

Many of the cases in one group merge with cases of other groups. This fact explains the difficulty in formulating a clinical picture for a disease which is so variable in its symptomatology.

The majority of these patients entered the hospital with complaints either directly or indirectly referable to the liver. The following analysis shows the variety of complaints together with the average duration of each:

Complaint	Number of Cases	Average Duration of
Vague gastrointestinal symptoms such as dyspepsia, anorexia, occasional vomiting, etc.	20	6 weeks
Ascites	19	9 weeks
Right upper quadrant pain	16	6 weeks
Weakness	10	2 months
Jaundice	9	4 weeks
Edema (dependent)	5	4 weeks (all in liver cell type)
Loss of weight	5	Unknown
Dyspnea	4	Indefinite
General abdominal pain	3	24 hrs. or less
Fever	2	1 week
Diarrhea	1	7 weeks
Hematemesis	1	1 day
Metastatic foci:		
Enlarged nodes of neck	1	1 month
Chest pain	5	1 month
Ulcer of eye	1	6 months

The usual case had two or three major complaints. However, patients with vague gastrointestinal symptoms, right upper quadrant pain (fre-

quently simulating that of cholecystitis) and rapidly accumulating ascites comprise the largest group of cases. Loss of weight as a symptom plays an apparently minor rôle, having been mentioned in only five cases. This may be explained on the basis of the counteracting gain of weight due to ascitic accumulation. Several patients sought medical attention because friends noticed their rapidly increasing girth. Rolleston [7] reports that two of his patients gained weight. This might well be explained on the basis of ascites. Edema, especially of the dependent sort, was complained of in only five cases, although it was found more frequently on physical examination. It usually appears late in cases of primary carcinoma of the liver and is of differential significance in those patients with complaints referable to cardiac decompensation. Often, it may be difficult to separate the symptomatology of one from the other. This was true in three of the above patients. Fever as a chief complaint was present in two cases only, one in each type of carcinoma. This will be considered in greater detail under clinical findings. Hematemesis occurred once only as did diarrhea. The former fact is of interest because of its higher incidence in uncomplicated cirrhosis of the liver. In primary carcinoma of the liver, the course, as will be emphasized, is much shorter from the onset of symptoms to exitus than is that of cirrhosis of the liver. Collateral circulation is not as well established, therefore, as it is in cirrhosis of the liver.

Course

The average course from onset of symptoms to death was 3.2 months. Taken individually, that for the liver cell type was 2.5 months, that for the bile duct type 4.17 months. In ten cases the course was not ascertainable. These figures are unsatisfactory. No definite point of onset of the carcinomatous transformation could be ascertained. In many patients symptoms were masked or so negligible that they were not mentioned. Having no definite point of inception of the malignant process to compute from, the known time of onset of the more severe complaints was used as the criterion from which to estimate the onset of the disease. However, one does learn from these figures that the duration of the illness from the onset of symptoms to death is a short one, more so in the liver cell type than in the bile duct type. The extent of liver involvement seems to be correlated with the length of life. Those patients who show less extensive involvement of the liver pursue a somewhat longer course, as do those in whom the cirrhotic process in the liver is less severe.

Etiology

Karsner,[8] reviewing nine cases clinically and pathologically, considered several factors as possible contributing causes, among which were alcohol, tobacco and opiates. Syphilis was not mentioned in any of his cases. In the present analysis it was impossible to consider all these factors inasmuch

as reference to many of them was not made. However, syphilis and alcohol were mentioned either in the affirmative or negative in the majority of instances.

In ten cases of the present series, nine of which were of the liver cell type, indications of syphilis were present, such as positive Wassermann reactions, positive histories and affirmative postmortem findings. In 22 patients a history of overindulgence in alcohol was obtained. Nine were heavy drinkers either in the past or at the time of admission. The remainder of the 22 patients fell in the class of moderate drinkers. In ten cases no information was available on this point. Here also the evaluation can readily be seen to be extremely difficult because of the personal equation involved. The distribution of the cell types was approximately equal. No notation on any of the above cases was made as to the incidence of pellagra, peripheral neuritis or beriberi.

The physical findings varied greatly. In some instances no physical changes referable to carcinoma of the liver were detectable. In others, the findings were more indicative of pathological changes in the liver.

General Appearance: In spite of the absence of loss of weight in the majority of the patients, emaciation or signs of poor nutrition were recorded in the greater percentage.

Jaundice: Jaundice was present in 32 patients, or in 51.6 per cent, at some time during their hospitalization. It was usually mild in type. There was a noticeably higher incidence of jaundice in the bile duct than in the liver cell type, 57.1 per cent in the former, 46.1 per cent in the latter. This, compared with the incidence of jaundice in cirrhosis of the liver, is higher, that in cirrhosis being less than 30 per cent of all cases at some time in their course, and then usually slight and frequently transient. Jaundice was relatively infrequent in the massive type of primary carcinoma. The reasons for this will be evident after consideration of the naked eye pathological changes.

Ascites: Ascites was present in 28 cases, or in 45.2 per cent. The incidence was about equal in both the bile duct and liver cell types.

Hepatomegaly: The percentage of patients in whom the liver was either palpable or enlarged on percussion was 70.0 per cent, or in 44 cases. In a large number of patients the presence or absence of nodularity was difficult to determine because of ascites. However, it was mentioned in 28 of the 44 cases. The liver was tender in only five cases. Rolleston states that as a rule, patients with cirrhosis of the liver and carcinoma complain oftener of tenderness than those without carcinoma. This statement is not borne out in the present series where the liver was tender in a minority of patients. Patients with carcinoma complained of pain more frequently, usually located in the right upper quadrant, than those with portal cirrhosis alone. This fact has been mentioned by several writers.

Splenomegaly: The spleen was palpable in one case only. This in part was probably due to interference by ascitic accumulation.

Dependent edema was present in eight cases. In all of them there was ascites as well.

Hemoglobin determinations and red blood counts were done in 20 cases. The average in these cases was 73 per cent hemoglobin with 3.41 million red blood cells, the extremes varying from 49 to 96 per cent hemoglobin and 2.51 to 5.1 million red cells. White blood counts were done in 25 cases, the average count being 10,920, the extremes varying from 7000 to 21,800. Icteric indices were done in several cases but no conclusions appear to be justifiable in so small a number of determinations.

Temperature: Fever was observed in 29 cases. This, as a rule, was mild, varying from 99 to 101 degrees Fahrenheit. In four patients in whom the temperature reached a higher level, clinical signs of pneumonia were present. In short, fever was present in 25 patients in whom no findings referable to infection or other source of fever were found. This constitutes 47.3 per cent, inasmuch as nine cases ran no clinical course. This figure is somewhat lower than that reported by others.

Pathology

Classification: The gross pathological changes in the liver comprise, first, those of the tumor itself and second, those of the associated cirrhosis, when present. According to the classification of Eggel, the 62 cases in this series fall into the three groups as follows:

Massive type	13 cases, nine of which were of liver cell and four of bile duct origin.
Multinodular type	37 cases, 23 of which were of liver cell, 12 of bile duct, and two of dual origin.
Diffuse type	12 cases, six of which were of liver cell and six of bile duct origin.

The above figures show the preponderance of the multinodular type over the combined diffuse and massive types. A still larger number of cases, however, might well have been classified as of the massive type had it not been for the fact that many small secondary nodules were present in the left lobe of the liver.

Cirrhosis of the Liver: The association of cirrhosis of the liver in these cases is frequent. Eggel reports an incidence of 85 per cent of cirrhosis of the liver in primary liver cell carcinoma, and 59 per cent in the bile duct type. Karsner reports cirrhosis in the nine cases studied by him, four of which were of liver cell origin, and five of bile duct origin. In the present series many cases were diagnosed by the naked eye as combining primary carcinoma and cirrhosis of the liver. However, on microscopic examination several fallacies became apparent. First, as mentioned by Eggel, is the desmoplastic reaction to the tumor growth that is present in both forms, although it is more severe in the bile duct type. In order to ascertain the presence or absence of cirrhosis, one must take sections far enough from the tumor tissue in order to exclude desmoplastic reaction. Second, the

pressure of tumor nodules, together with necrosis of surrounding tissue and subsequent fibroblastic reaction, must be considered in determining the presence of a cirrhotic process. One must examine uninvolved tissue to exclude these factors. Third, biliary obstruction due to tumor encroachment on bile radicles frequently causes fibrosis of liver tissue. In such situations, however, the fibrosis is usually biliary in origin rather than portal.

With the above facts in mind, an attempt was made to ascertain the incidence of cirrhosis of the liver in the present series. In some instances it was impossible to make this decision because of the presence of tumor tissue throughout the liver. These cases were usually of the multinodular type. They were six in number. It was found that 25 of the 39 cases of carcinoma of the liver cell type, or 64.1 per cent, were attended by some degree of cirrhosis, while only seven of 21 cases of bile duct origin, or 33.3 per cent revealed detectable cirrhosis. These figures are somewhat lower than those of Eggel's. His cases, however, were collected in greater part from different sources, and many of them were classified without benefit of microscopic examination.

Microscopic Types of Carcinoma: As already mentioned, there are three microscopic types of primary carcinoma of the liver—the liver cell, bile duct and dual or indeterminate.

The liver cell type of carcinoma is composed of strands and cords of large polygonal cells with pinkish cytoplasm and large round vesicular nuclei frequently having one or two nucleoli. These cells are arranged in cords and may even simulate lobules of liver tissue. The cells at the edges of the tumor nodules may frequently be traced in the process of transition from apparently normal liver cells. No central veins are discernible in these tumor nodules, but bile is often present in the intercellular spaces and in the accompanying biliary radicles which, in some instances, show marked proliferation. The formation of giant cells by amitotic division is frequent. There are usually moderate or even marked signs of anaplasia, characterized by variations in the size and shape of the cells as well as in their staining properties. In the majority of these cases tumor invasion of the veins and lymphatics may be detected microscopically.

The bile duct type of tumor, in contrast to the liver cell type, assumes the appearance of an adenocarcinoma, the lining cells varying from low cuboidal to tall columnar, depending on their origin from the smaller or larger biliary radicles. The cytoplasm is usually clear, somewhat basophilic, with round or oval, hyperchromatic nuclei. Nucleoli and giant cells are much less frequent than in the liver cell type. At times the structure of the tumor may vary from simple bile duct proliferation to that of a true adenocarcinoma. There is a more marked desmoplastic reaction in the bile duct than in the liver cell type. As in the liver cell type there is evidence of invasion of veins and lymphatics by tumor tissue.

In both types there is usually moderate lymphocytic reaction in the stroma. This is pronounced in cases associated with cirrhosis of the liver.

The dual or indeterminate type is rare. The fact that in this type differentiation is so irregular suggests a higher degree of malignancy as far as microscopic evidence may be depended upon to estimate the degree of malignancy of any tumor. However, with only two cases from which to draw conclusions, little can be said on this point with any measure of certainty. Both cases in question, however, metastasized to the lungs. This fact supports the view that tumors of dual origin tend in the direction of a somewhat exalted degree of malignancy.

Hemochromatosis: No figures on the incidence of hemochromatosis in primary carcinoma of the liver are available. In the present series there were encountered six cases, or an incidence of 9.9 per cent. In all six cases there was an associated cirrhosis of the liver. However, there were only a total of 32 cases in the 62 cases of this series which had cirrhosis of the liver. This, therefore, would give an incidence of 18.7 per cent of hemochromatosis in those cases of primary carcinoma of the liver associated with cirrhosis. The incidence is noticeably higher than that of hemochromatosis in cirrhosis of the liver without primary carcinoma which has been variously reported as occurring in 7 to 10 per cent of all such cases.

Size of Liver: The size of the liver was mentioned in 48 of the 62 cases of primary carcinoma in this series. The average was 2900 grams. In four the liver was mentioned as " normal " or " small "; in eight as " large " and in one case no mention was made of the size. The average size of the liver in 30 cases of the liver cell type was 2834 grams, while that in 17 cases of the bile duct type was 2990 grams.

Ascites: Ascites was present in 45 cases, or in 72.6 per cent—the most constant finding of the series. This varied in amount, averaging three to four liters. The ascites was bloody in six cases, two of which showed superficial necrosis of tumor nodules with rupture and hemorrhage. In seven others ascites was serosanguinous in character.

Splenomegaly: Splenomegaly was present in the majority of cases. In 39 of the 62 cases where the weight was mentioned, the average was 354 grams, and was slightly higher in the bile duct type. In 13 cases the spleen was mentioned as " normal " in size, while in six it was " enlarged." No mention of size was made in four cases. It has been said that the incidence of splenomegaly is in direct proportion to that of neoplastic thrombosis of the portal or splenic veins. In 27 cases of the liver cell type analyzed in this paper, the average weight of the spleen was 331 grams. Of these, 11 showed neoplastic venous thrombosis, 10 involving the portal vein (and, in three of them, the splenic vein as well), and in one case intrahepatic venous channels. Sixteen had no naked eye evidence of thrombosis. In one of the 11 cases with venous thrombosis, the spleen weighed 90 grams. In the others it weighed over 150 grams. In 12 cases of the bile duct type the

average weight of the spleen was 380 grams. Neoplastic venous thrombosis was mentioned in three and in all of them the spleen weighed over 150 grams. The heaviest spleen in the entire series weighed 900 grams and showed no naked eye evidence of tumor thrombosis of any part of the portal system. The explanation of the splenomegaly on the basis of portal obstruction is supported by the fact that, on microscopic examination in the majority of cases, venous invasion was evident. This, together with the degree of portal cirrhosis, explains the higher incidence of splenomegaly and ascites in carcinoma than in cirrhosis of the liver alone.

Jaundice: The incidence of jaundice was the same clinically and post mortem. Jaundice was explainable in the majority of cases on the basis of biliary obstruction by pressure from tumor nodules. This point is borne out by the infrequency of jaundice in cases of the massive type, that is to say, those which were not attended by secondary nodules. In other instances jaundice was due to widespread destruction of liver tissue by tumor growth.

Metastases: The secondary spread of primary carcinoma of the liver takes place by direct extension and by metastasis through the blood and lymph channels. Solitary distant metastases to brain, bone, kidney, etc., are not uncommon. In 19 cases, or in 30.6 per cent, naked eye evidence of neoplasmic venous thrombosis was present. In several cases this process involved two or more of the larger venous channels leading to or from the liver. In six of the 19 cases there were visceral metastases likewise visible to the naked eye. The tumor thrombi were not adherent to the wall of the vessel but were composed of organized and laminated blood clot in which were strands and masses of tumor tissue. In two cases, tumor thrombi were found to have travelled through the inferior vena cava into the right auricle of the heart. In several, the splenic vein was thrombosed throughout its entire length. In 29 cases, or in 46.8 per cent of the entire series, there was no naked eye evidence of metastasis. In the remaining 33 the sites of metastases were numerous. The most frequent were the periportal lymph nodes and the lungs, especially the right lung. The reason for this is evident when one appreciates the frequency of venous and lymphatic invasion by these tumors. On the contrary, it is amazing that so many cases exhibit freedom from metastases in spite of the high incidence of venous and lymphatic neoplasmic invasion.

The following table shows the sites of metastases in both types.

In connection with the general subject of metastasis in primary carcinomata of the liver, it is interesting to note that Bolker[9] and his associates recently reviewed the literature with especial reference to the occurrence of bone metastases. They found only nine such cases recorded. In the present series three examples of metastasis to bone were noted. In one case the metastases were multiple and involved ribs, vertebrae and the left orbital bone; in the other two ribs alone were involved. In another case of this series the spleen was invaded by retrograde growth through the splenic

	Liver Cell Type	Bile Duct Type	Total
Lung	9	5	14
Pleura	2	1	3
Lymph nodes:			
Hilar (portal)	6	3	9
Mesenteric	5	1	6
Mediastinal	0	2	2
Inguinal	1	0	1
Cervical	2	0	2
Omentum	1	0	1
Kidney	2	0	2
Adrenal	1	2	3
Pancreas	2	1	3
Stomach	1	1	2
Peritoneum	1	2	3
Heart muscle	0	1	1
Bone:			
Ribs	3	0	3
Vertebra	1	0	1
Orbital bones	1	0	1
Spleen	1	0	1
Eye	1	0	1

vein. The size of the spleen was not mentioned. Involvement of the heart muscle occurred once by direct extension through the pericardium from a metastasized mediastinal node.

Comment

Only seven of the above 62 cases were diagnosed clinically. The diagnoses entertained in order of frequency were (1) carcinoma of the stomach with metastasis to the liver; (2) cirrhosis of the liver; (3) carcinoma of the head of the pancreas; (4) "malignancy" of the liver, primary site undetermined; (5) cardiac decompensation. In the remaining 55 cases there is no available data to show that the possibility of primary carcinoma of the liver was even suggested. It would seem that the diagnosis should be made more often if its relative frequency is borne in mind. Symmers, at Bellevue Hospital, correlating 20 years' experience in the necropsy rooms and in the wards, has successfully made the clinical diagnosis in seven instances based on the following criteria:

(1) A male patient over thirty-five years of age.
(2) A large palpable tumor mass in the right lobe of the liver.
(3) No primary tumor discoverable elsewhere.
(4) Jaundice, usually mild.
(5) Ascites.
(6) An otherwise unexplainable fever of mild degree.

It was found that each of the 62 cases fulfilled at least four of the above criteria and in the majority of cases five or even all of them. The author believes that a history of either vague gastrointestinal nature of short dura-

tion or signs of portal obstruction in the form of rapidly accumulating ascites should be used as additional information.

The history of rapidly accumulating ascites in primary carcinoma of the liver is in contra-distinction to that of ascites due to other causes—cardiac failure, tuberculosis or carcinomatosis of the peritoneum, etc. In ascites of cardiac origin evidence of its cause is practically always available. In ascites of peritoneal origin due to carcinoma, tuberculosis or the like, findings indicative of its cause are likewise apt to present themselves. On the other hand rapidly accumulating ascites may be due to thrombosis of the portal vein of variable origin. In this connection it is to be recalled that neoplastic thrombosis of the portal vein not infrequently occurs in association with primary carcinoma of the liver.

Summary and Conclusions

1. Primary carcinoma of the liver, formerly regarded almost in the light of a curiosity, is shown in this paper to occur once in every 394 necropsies, an incidence of 0.25 per cent based on 24,400 consecutive necropsies performed at Bellevue Hospital over an unbroken period of 30 years. The Bellevue series consists of 62 cases, in every one of which the diagnosis was verified by microscopic examination. It is believed to be the largest series thus far derived from a common source.

2. Primary carcinoma of the liver is a clinical and pathological entity susceptible of diagnosis during life.

3. The clinical diagnosis may be postulated with reasonable certainty on the following criteria (Symmers): (a) the presence of a palpable massive solitary growth in the right lobe of the liver in a male over 35 years of age, (b) inability to determine a primary growth in any other part of the body, (c) jaundice, usually of a mild grade, (d) ascites and (e) a low degree of otherwise unexplainable fever. In addition to these criteria a preliminary history of vague gastrointestinal disturbances of short duration or signs of portal obstruction extending over a period of a few weeks only, should likewise be taken into consideration (Gustafson). Clinically, the disease pursues a rapid course, death occurring, as a rule, within three to four months after the onset of detectable symptoms and signs.

4. In the Bellevue series of 62 cases of primary carcinoma of the liver, 32, or 51.6 per cent were associated with cirrhosis of the liver, including six cases of hemochromatosis of the liver with cirrhosis.

5. Microscopically, 39 of the 62 cases studied at Bellevue Hospital were obviously derived from the liver cells and 21 from the bile ducts; 2 were of indeterminate or dual origin. The liver cell type is characteristic. It has multiple points of origin and its cell constituents may be traced directly into neighboring apparently normal parenchyma cells. The bile duct type, as should be expected, is histologically indistinguishable from the duct cell carcinoma of the pancreas.

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THE CLINICAL USE OF CRYSTALLINE INSULIN *

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SINCE the discovery of insulin by Banting and Best,[1] unremitting effort has been put forth toward the improvement of the product. One of the lines of endeavor has been to make insulin purer by crystallization.

Insulin was first crystallized by Abel [2, 3, 4] in 1926. He prepared it from highly purified commercial preparations. Howard and DeLawder [5] were the first to determine whether this crystalline insulin could be used therapeutically in human beings for the treatment of diabetes mellitus. Four diabetic patients were carefully regulated on diets and standard insulin; then crystalline insulin was substituted for standard in equivalent doses. They observed no appreciable difference except for a slight increase in carbohydrate tolerance which they thought could be expected in diabetic patients under treatment.

Until recently crystalline insulin was not used clinically because the yield of this insulin was small and it was therefore not commercially practical. In February of 1936, however, a new method of crystallizing insulin was developed by Dr. Melville Sahyun, of Detroit, which was practical for commercial use. We had the opportunity of making clinical trials of this crystalline insulin and found it to be suitable for the treatment of diabetes.[6]

Comparative studies were then made of standard commercial and of crystalline insulin. These studies were conducted with 20 patients and the conclusions were that crystalline insulin could be used in the treatment of diabetes mellitus and that with its use the blood sugar levels could be controlled with fewer doses and fewer units of insulin than was the case with standard insulin. Freund and Adler,[7] Mains and McMullen,[8] and Barach [9] have reported similar results.

During the past year we have used crystalline insulin in the treatment of 100 diabetic patients who range in age from six to 86 years and who present a variety of complications. Some of these patients were being treated in the hospital as in-patients; some were treated in the clinic as out-patients, and the rest were private patients seen in the office.

The results of this year's work are summarized in tables 1 and 2. The former shows the number in each age group and the incidence of complications; the latter, the various types of complications present.

It is well known that in children and adolescents the treatment of diabetes with diet and standard insulin abounds in difficulties. The attempt to keep the blood sugar within normal limits necessitates a great deal of adjustment of amount of insulin and time of administration to prevent hypoglycemic reactions.

* Read at the St. Louis meeting of the American College of Physicians, April 22, 1937.

TABLE I

One Hundred Diabetic Patients to Whom Crystalline Insulin Was Given

Age Group	With Complications	Without Complications	Total
1–20	2	8	10
21–40	5	14	19
41–60	39	7	46
61 and over	15	10	25
Totals	61	39	100

TABLE II

Types of Complications Present in Diabetic Patients in This Study

Infections	Respiratory
	Lues
	Tuberculosis
	Osteomyelitis
	Carbuncle
	Ulcers of legs
	Acute iritis
Cardiovascular	Hypertension
	Cerebral hemorrhage
	Hemiplegias
	Coronary thrombosis
	Heart disease
	Hypertensive
	Arteriosclerotic
	Rheumatic
	Gangrene
Gastrointestinal	Peptic ulcer
Neurological	Neuritis
	Epilepsy
	Parkinson's disease
Ophthalmological	Cataracts
	Neuroretinitis with blindness
Other complications	Pregnancy
	Acidosis
	Uremia
	Pre-operative and post-operative

The 10 patients in our youngest group, those under 20 years of age, were successfully treated with crystalline insulin. Two were controlled with one dose daily; eight were controlled with two doses administered from 10 to 12 hours apart, the morning dose given one-half to one hour before breakfast and the evening dose either before or after the evening meal according to the individual indications. Seven of these children were attending school, and elimination of the noon dose of insulin—and in one case of a midnight dose also—was greatly appreciated. In this group two of the patients presented complications. A boy of seven had an active childhood tuberculosis with a daily rise in temperature. A girl of 19 had an infection of

the right index finger with osteomyelitis of the distal phalanx, due to a needle prick.

The second group, 21 to 40 years of age, included wage-earners and housewives. All of the patients in this group were given crystalline insulin in two doses, at 10 to 14 hour intervals. The advantage of being able to go without a noon dose is very obvious in the cases of persons working in factories or offices. One of the young women in this group has pulmonary tuberculosis and she had found it a great hardship to have her sleep interrupted nightly for a 1 a.m. dose of insulin. With crystalline insulin, however, she has been able to keep her diabetes under control with two doses given 14 hours apart—at 8 a.m. and 10 p.m.

The age group from 41 to 60 years included a good many patients manifesting various types of arteriosclerotic complications—coronary heart disease, hemiplegias, ophthalmoplegia, blindness due to vascular changes, hypertension and gangrene. There were also some other types of complications: cataracts, lues, tuberculosis and acute iritis. Arteriosclerotic manifestations were also present in the group from 61 to 86 years of age.

In the care of elderly diabetic patients with cardiovascular complications, it is especially important to prevent hypoglycemic reactions. Rapid reduction of the blood sugar level in this type of patient has been the cause of cerebral thrombosis, coronary thrombosis, visual disturbance due to thrombosis in the vessels of the fundi, and thrombosis in the peripheral vessels of the extremities. It would be difficult to estimate the mortality rate for the unskillful use of insulin. For this reason, in making clinical studies of insulins, it is just as important to judge the control of the diabetes from the standpoint of hypoglycemia as from that of hyperglycemia and glycosuria.

We have used crystalline insulin successfully pre-operatively and post-operatively in two cases, and also in the cases of three patients with acidosis. In these conditions, where glucose was administered every four hours either by mouth or intravenously, crystalline insulin was given every eight hours and the doses were determined by urine and blood examinations.

Crystalline insulin is administered subcutaneously in one or two doses. The morning dose is given one-half to one hour before breakfast and the second dose—if such is necessary—is given 10 to 14 hours later, either before or after the night meal depending upon the circumstances of the patient's eating arrangements. In a patient whose insulin requirement is unknown, we start with an arbitrary amount, 10–0–10, and adjust the dose according to the urine and blood examinations. If the patient had previously been on standard insulin, he is started on two-thirds of that amount of crystalline insulin divided into two doses.

In the entire group of patients to whom crystalline insulin has been given it has been noted that when there is an insulin reaction it comes about gradually unassociated with any shock. An opportunity afforded itself to note comparative shock effects of standard and of crystalline insulin in a

study of the use of insulin in the treatment of schizophrenia by our psychiatric department. Four non-diabetic schizophrenic patients were given insulin to produce shock. Sixty to 80 units of standard insulin produced a severe shock in all four patients; but 100 units of crystalline insulin did not cause any shock to three of the patients, and resulted, in the case of the fourth patient, in a light coma which was very readily relieved. Another observation was that with crystalline insulin it was possible to produce much lower blood sugar levels without resulting coma than was possible with standard.

Among the patients to whom crystalline insulin was administered no local reactions were observed. Ordinarily such reactions, which are considered allergic, may be expected in about 5 to 10 per cent of diabetic patients treated with insulin. It has been reported that crystalline insulin Abel [10] and crystalline insulin Scott [11] have caused allergic reactions in certain sensitive individuals but much less so than noted with the standard commercial preparations. Perhaps after we have used crystalline insulin in a larger number of cases, we may also encounter allergic reactions. Crystalline insulin is a protein and therefore might cause reactions, but being a purer pancreatic extract, it is less likely to contain other pancreatic proteins than is standard insulin.

The condition of lipodystrophy which is noted occasionally at the site of insulin injection was present in three of our patients, and was very marked in two, producing deformed looking arms and thighs. The use of crystalline insulin over a period of 18 months has not produced this subcutaneous atrophy of the tissues in these patients.

From a year's experience with crystalline insulin, we have concluded that it can be used in any type of diabetes requiring insulin, with or without complications, except in diabetic coma with which condition we have not had any experience. Crystalline insulin is remarkably stable. We observed no clinical evidence of deterioration in a solution kept at room temperature for as long as a year.

Since Abel first crystallized insulin, studies have been made of its physiological, physical and chemical properties. Some of the findings offer a possible explanation for the greater efficiency of crystalline than of standard insulin. Observations have been recorded of a preliminary hyperglycemia following the injection of standard insulin, which led to investigations to determine whether this hyperglycemic action is a property of insulin or whether there is a secondary accompanying substance in the insulin. Burger and Kramer,[12-21] who have made a large number of chemical and physical comparative studies, believe that they have been able to isolate a hyperglycemic principle from standard insulin which they call Glukagon. Their studies show that this principle is not present in crystalline insulin. Geiling and DeLawder [22] investigated this point and concluded that the hyperglycemic action was due solely to impurity and that crystalline insulin did not

produce any preliminary hyperglycemia because of the absence of this impurity. Tangl and Than [23] confirmed the presence of such impurities in standard insulin by isolating a pancreatic extract possessing marked hyperglycemic properties.

Thus, evidence points to the presence of a substance in standard insulin, whether it be a separate hormone or an impurity, which causes hyperglycemia, and so obviously must decrease the efficiency of the insulin. This substance is not present in crystalline insulin. This seems a logical explanation of the greater efficiency of crystalline insulin than of standard.

Summary

Crystalline insulin has been used in the treatment of diabetes in 100 patients ranging in age from 6 to 86 years. Sixty-one of these patients had various types of complications; 39 were without complications. In some of these patients the diabetes was well controlled with one dose of crystalline insulin. None of them required more than two doses which were administered 10 to 14 hours apart.

Insulin reactions were rare, and when they did occur were not associated with as much shock as is experienced with standard insulin; much lower blood sugar levels were obtained without manifest symptoms of reaction. No local reactions were observed in this entire group. The condition of lipodystrophy, which was present in three patients following the use of standard insulin, was not observed when crystalline insulin had been in constant use for 18 months.

Possible explanations for the increased efficiency of crystalline insulin are presented.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING EXTERNAL CHEST INJURY TO DOGS *

By R. W. Kissane, M.D., F.A.C.P., R. S. Fidler, B.A., M.D., and R. A. Koons, B.A., M.D., *Columbus, Ohio*

Medical literature contains considerable evidence, obtained by autopsy, that non-penetrating wounds to the chest can produce severe traumatic lesions in the pericardium, heart and great vessels, but it is not generally accepted that less severe trauma can cause mild changes in the heart which have a tendency to recover.

Beck [1] described experiments on dogs where the heart was exposed and contused. The resultant myocardial injuries produced electrocardiographic changes similar to those obtained in coronary artery occlusion, affecting chiefly the Q- and T-wave and having a tendency to return to normal. Randles, Gorham and Dresbach [2] described alternation in the RS–T component of the electrocardiogram simulating those associated with coronary artery occlusion, produced in dogs by experimental auricular rupture and the resulting hemopericardium. It was their opinion that the variation of the RS–T component was due to the amount of fluid in the pericardial sac and not the auricular injury.

In order to ascertain whether electrocardiographic changes do occur following external chest injury, and if so, the type of changes, the speed with which they occur, the amount of required trauma and the lesions produced, a series of experiments was performed on dogs in which electrocardiographic and pathological studies were made following varying degrees of injury to the chest but not to the heart direct.

Protocols

Dog 1 (figure 1). A young mongrel dog, weight 30 pounds, was given 1 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. A ¾ inch board was placed over the sternum and one heavy blow was struck with a hard rubber mallet and electrocardiogram *B* was taken in five minutes. Ten minutes after the first blow, a second similar blow was struck in the same manner. This was followed by a jerky type of respiration using chiefly the external thoracic muscles. Electrocardiogram *C* was taken 10 minutes after, *D*, 20 minutes after, *E*, one and one-half hours after, *F*, two and one-half hours after, and *G*, five and one-half hours after the second blow. At this time the dog was killed by chloroform and an autopsy performed which revealed hemorrhage into the anterior and posterior mediastinal spaces and about the roots of both lungs. The microscopic examination revealed hemorrhagic infiltration of the lungs, a small hemorrhage beneath the endocardium at the base of the mitral valve and a small hemorrhage beneath the endocardium of one of the cusps of the pulmonary valve.

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Dog 2 (figure 2). A mongrel bitch, weight 35 pounds, was given 1 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. A ¾ inch board was placed over the upper sternum and two moderately heavy blows were struck with a hard rubber mallet and electrocardiogram *B* was

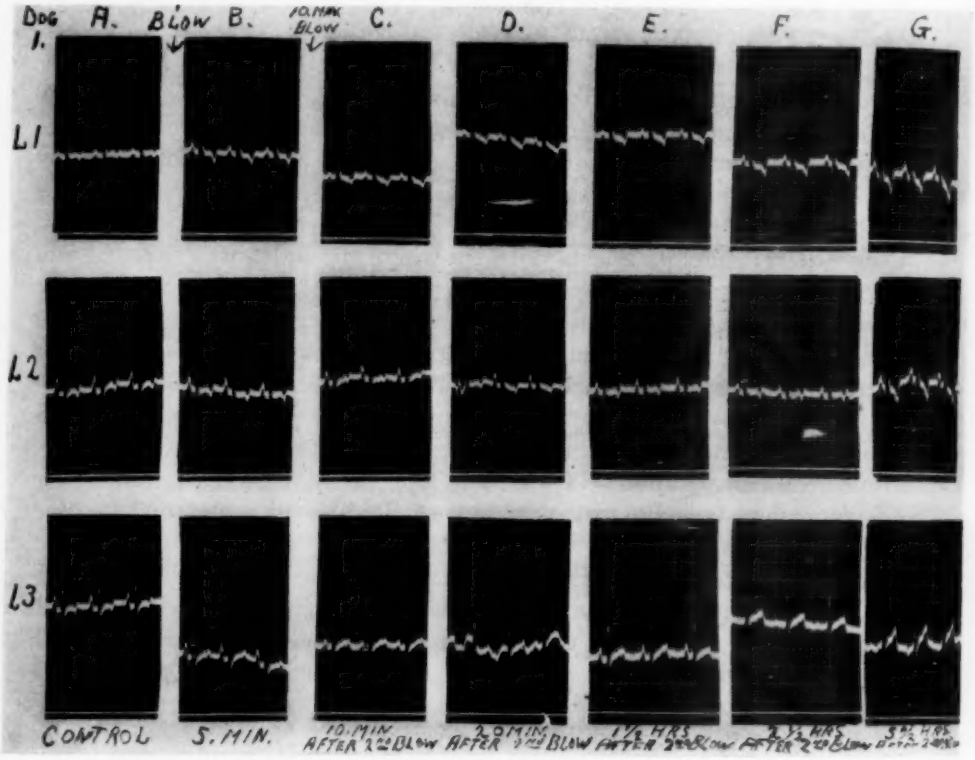

FIG. 1. Dog 1.

taken in 10 minutes, *C* in one hour, *D* in three hours and *E* in five hours. At this time another similar blow was struck and electrocardiograms *F*, *G* and *H* were taken 10 minutes, one-half hour and three-quarters hour later. At this time the animal was killed by chloroform and an autopsy performed which revealed no abnormal lesions of the heart but moderate atelectasis, congestion and a slight amount of hemorrhage of both lungs.

Dog 3 (figure 3). A young mongrel dog, weight 30 pounds, was given 1 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken, the sternum was now struck a heavy blow with an ordinary hammer and electrocardiograms *B*, *C* and *D* were taken five minutes, one-half hour and three-quarters hour later. At this time a second similar blow was struck and electrocardiograms *E* and *F* were taken in five minutes and in one hour. A third series of two similar blows was now struck and following these electrocardiograms *G* was taken in one-half hour and *H* in one hour. The animal was now killed by chloroform and an autopsy performed which revealed moderate hemorrhage and atelectasis about the right lung root.

Dog 4 (figure 4). A mongrel dog, weight 25 pounds, was given 0.75 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A*

was taken. A ¾ inch board was placed over the sternum and a heavy blow was struck with a 10 pound sledge hammer and electrocardiograms *B*, *C*, *D* and *E* were taken five minutes, one-half hour, one and one-half hours and two and one-half hours later. The animal was killed by chloroform and an autopsy performed that revealed small subendocardial hemorrhages into the right and left posterior cusps of the aortic valve.

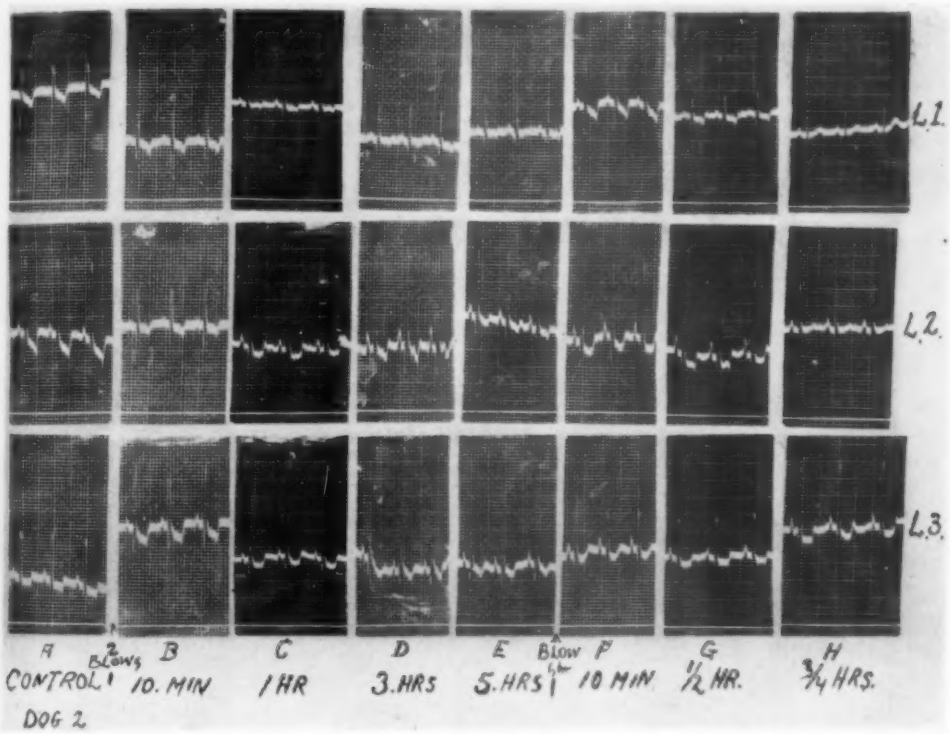

FIG. 2. Dog 2.

Dog 5 (figure 5). A young mongrel bitch, weight 24 pounds, was given 1 gm. of sodium amytal intraperitoneally and one hour and 15 minutes later the control electrocardiogram *A* was taken. A ¾ inch board was placed on the left chest over the point of maximal intensity of the apex beat and one full blow delivered with a 10 pound sledge hammer while the electrocardiogram was attached in Lead II with the camera running. The string was protected for only a second while the blow was struck, and immediately afterwards brought back into the camera field and standardized, revealing by the timer that electrocardiogram *B* was taken twelve seconds after the blow was struck (figure 6). Electrocardiogram *C* was taken in five minutes, *D* in one-half hour, *E* in one hour, and *F* in one and one-half hours after the blow was struck. Five minutes after the last electrocardiogram was taken a second blow was delivered in the same manner and the electrocardiogram *G* (figure 7) was taken within a few seconds. Electrocardiogram *H* (figure 8) was taken in 10 minutes, *I* in one and one-quarter hours, *J* in one and one-half hours, and *K* in two and one-half hours after the second blow. At this time the dog was killed by chloroform and an autopsy performed which revealed the peritoneal cavity filled with recent hemorrhage

originating from two tears in the liver, one in the dome of the right lobe which was 3 cm. long, 1 cm. wide and 2 cm. deep, and another upward from the gall-bladder 3 cm. and extending through the entire thickness of the liver at this point. There was no free hemorrhage in the pericardial sac but hemorrhage into the parietal wall of the pericardium anteriorly and into the tissues about the base of the heart. The microscopic examination did not reveal any abnormal lesions.

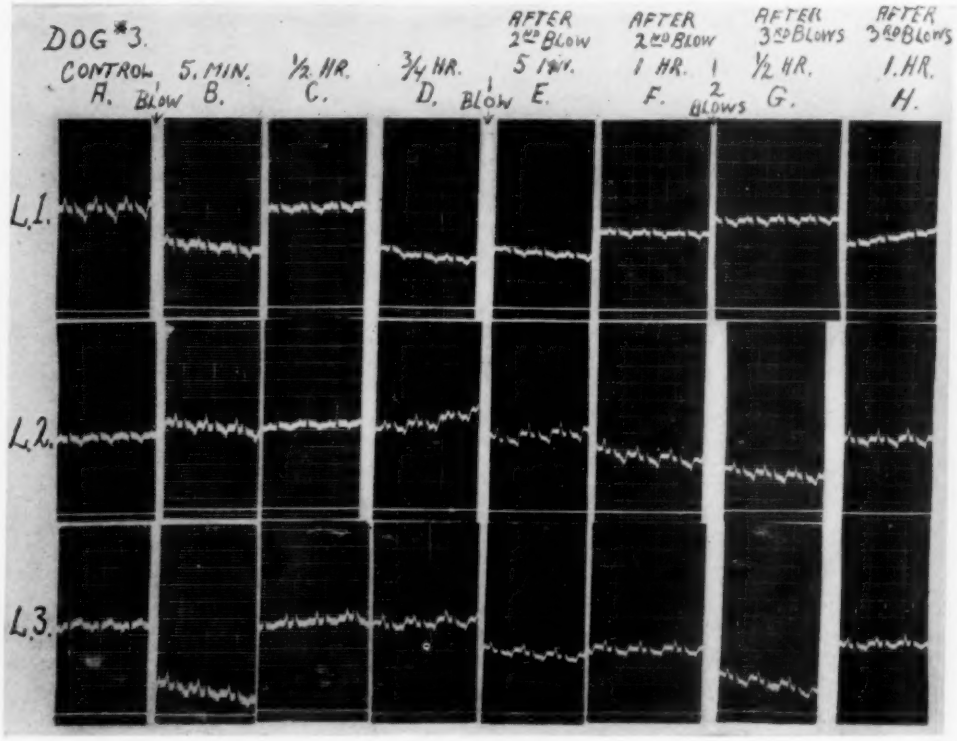

FIG. 3. Dog 3.

Dog 6 (figure 9). A mongrel dog, weight 60 pounds, was given 1.5 gm. of sodium amytal intraperitoneally and one and one-half hours later the control electrocardiogram *A* was taken. A ¼ inch board was placed over the left chest of the dog and one hard blow was struck with a four pound hammer, and one minute later electrocardiogram *B* was taken. Fifteen minutes after the first blow electrocardiogram *C* was taken and a minute later another blow was struck in the same manner, then one minute after the second blow electrocardiogram *D* was taken. Fifteen minutes after the second blow electrocardiogram *E* was taken, and one minute later two blows were delivered in the manner described and electrocardiogram *F* was taken one minute after the third series of blows. After a 15 minute period electrocardiogram *G* was taken and again, one minute later, two more blows were delivered in the manner described and the electrocardiogram *H* was taken in one minute, and *I* in 15 minutes after this fourth series of blows. At this time the dog, still under anesthesia, was taken to a veterinary hospital where he shortly regained consciousness but was found dead in his cage 10 hours later. At autopsy there was found a clean-cut one inch tear in the anterior parietal pericardium, with a moderate amount of free

hemorrhage in the pericardial sac, and a four inch rent in the posterior part of the right diaphragm. There was a contusion with a marked degree of hemorrhage of the entire right lung and of the base of the left lung. Shortly before the dog died the respiration was very rapid and shallow, temperature 106,° heart sounds normal, but many moist râles were heard throughout the chest. Microscopic examination revealed moderate atelectasis and hemorrhagic infiltration of the lungs.

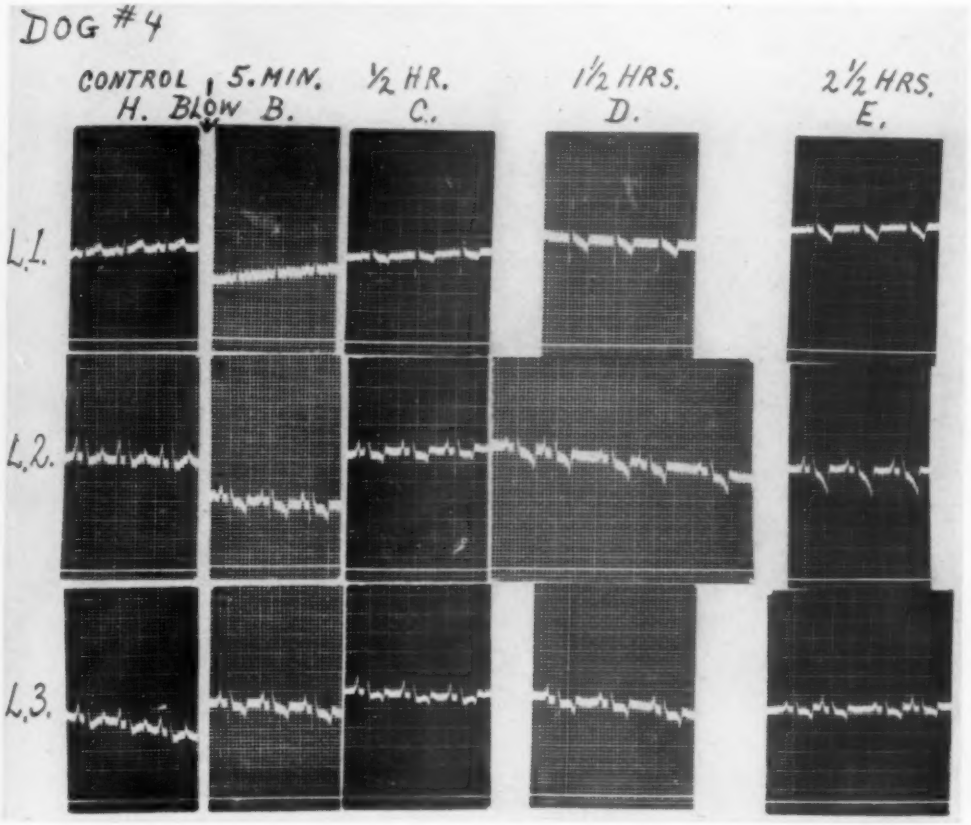

FIG. 4. Dog 4.

Dog 7 (figure 10). A hound dog, weight 35 pounds, was given 0.75 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. One hard blow was struck with a five pound hammer to the point of maximal cardiac pulsation on the left chest, and after 25 minutes electrocardiogram *B* was taken, and after two hours electrocardiogram *C* was taken. The dog was now taken to a veterinary hospital. There was no increase in the respirations nor any elevation of temperature, and the heart sounds appeared normal. The next day the dog was up and about, and appeared normal. There were no signs of tenderness on the chest wall. On the sixth day electrocardiogram *D* was taken and on the seventh day the dog coughed and spit blood, passed blood in the stool and had five attacks of syncope. On the eighth day electrocardiogram *E* was taken, and on the twenty-first day electrocardiogram *F* was taken. At this time the veterinarian reported that following exercise the dog would have an irregular heart rhythm.

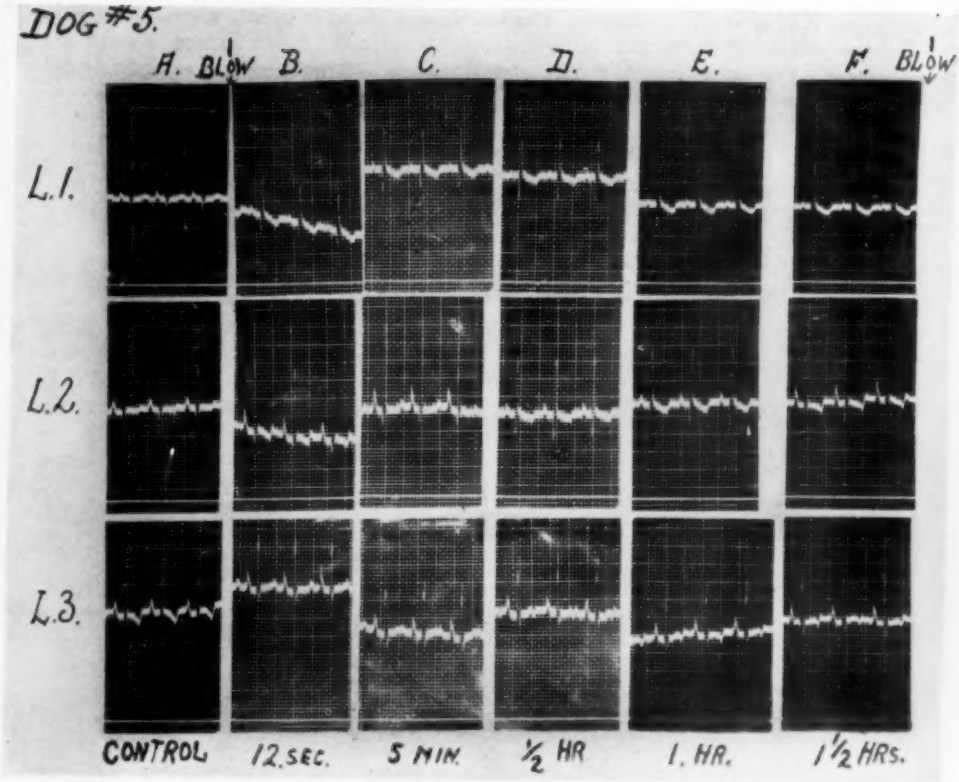

FIG. 5. Dog 5.

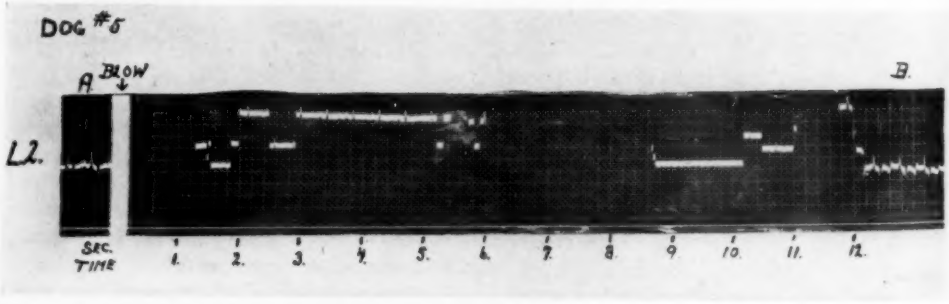

FIG. 6. Dog 5. A (control) is the same as A in figure 5. B, 12 seconds after blow, same as B in figure 5.

Electrocardiogram *G* was taken on the fortieth day and *H* on the one hundredth day after the blow was delivered, and on the one hundred and twenty-first day the dog suddenly dropped dead. An autopsy revealed no gross abnormal lesions except that the anterior parietal pericardium was slightly thickened. A microscopic examination revealed partial atelectasis, slight congestion and moderate hematogenous pigmentation of the lungs. The left coronary artery showed moderate subintimal and medial thickening with a vacuolization and loss of elastic tissue fibers.

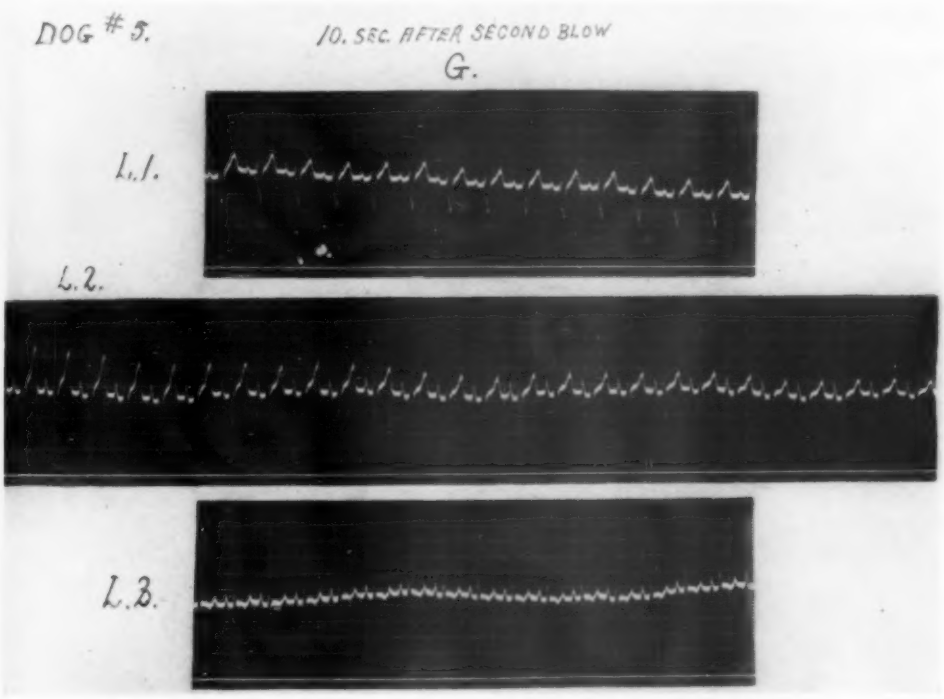

FIG. 7. Dog 5. Lead II taken first, Lead I second and Lead III last.

Dog 8 (figure 11). A short haired mongrel bitch, weight 22 pounds, was given 0.50 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. Following this two hard blows were struck with a five pound hammer on a ¾ board placed over the area of maximum intensity of the apex beat on the left chest, and one minute later electrocardiogram *B* was taken. At this time respiration ceased for a short period and then started with an irregular rhythm. Twenty minutes after the blows were struck electrocardiogram *C* was taken, and 50 minutes after electrocardiogram *D*. The dog was then taken to the veterinary hospital. The next morning she was up and about, apparently normal. On the second day after the start of the experiment electrocardiogram *E* was taken, and on the third day the animal died during sleep. An autopsy revealed no injury to the anterior chest wall, though there was a small hole in the anterior pericardium with about 5 c.c. of blood in the pericardial sac. There was no hemorrhage in the anterior or posterior mediastinal spaces, and a microscopic examination did not reveal any abnormal lesions.

Dog 9 (figure 12). A hound bitch, weight 26 pounds, was given 0.75 gm. of sodium amytal intraperitoneally and 45 minutes later the control electrocardiogram *A*

was taken, and following this two hard blows with a five pound hammer were struck on a ¼ inch board placed over the area of maximum intensity of the apex beat on the left chest. One minute after these blows electrocardiogram *B*, and 45 minutes after electrocardiogram *C* were taken. The animal was then taken to the veterinary hospital, and the next morning she was up and about, apparently normal. On the seventh day after the start of the experiment electrocardiogram *D* was taken, and on the sixteenth day the animal was found dead. An autopsy did not reveal any gross

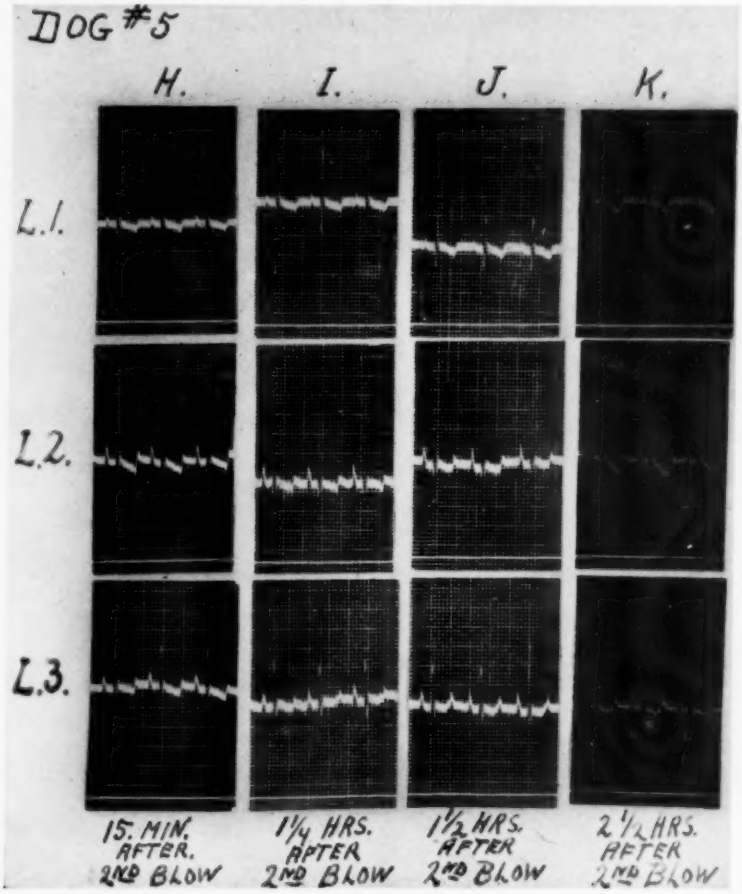

FIG. 8. Dog 5.

abnormal lesions, and a microscopic examination showed moderate congestion of the lungs and a moderate number of heart failure cells.

Dog 10 (figure 13). A German Shepherd bitch, weight 45 pounds, was given 1.5 gm. of sodium amytal intraperitoneally, and one hour later the control electrocardiogram *A* was taken. Two hard blows with a five pound hammer were struck directly on the area of maximum intensity of the cardiac apex beat on the left chest and electrocardiogram *B* was taken in one minute, *C* in two minutes, *D* in three minutes, *E* in four minutes, *F* in five minutes, *G* in seven minutes (figure 14), *H* in eight minutes, *I* in 12 minutes, *J* in 13 minutes, *K* in 14 minutes, *L* in 15 minutes, and *M* in 16 minutes following the blows. At this time the animal died and an autopsy

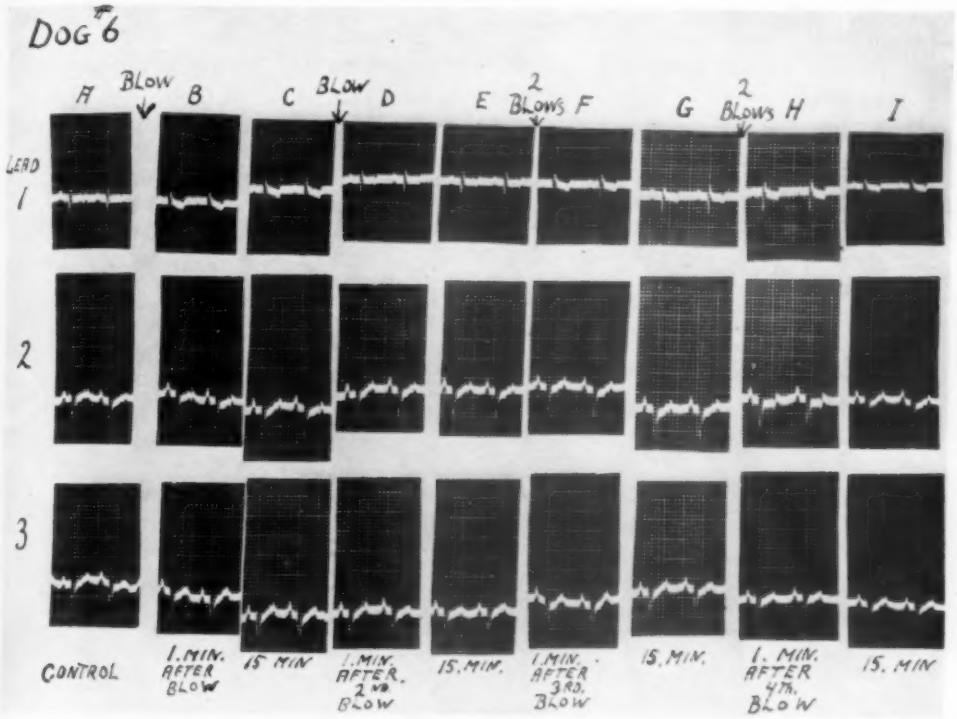

FIG. 9. Dog 6.

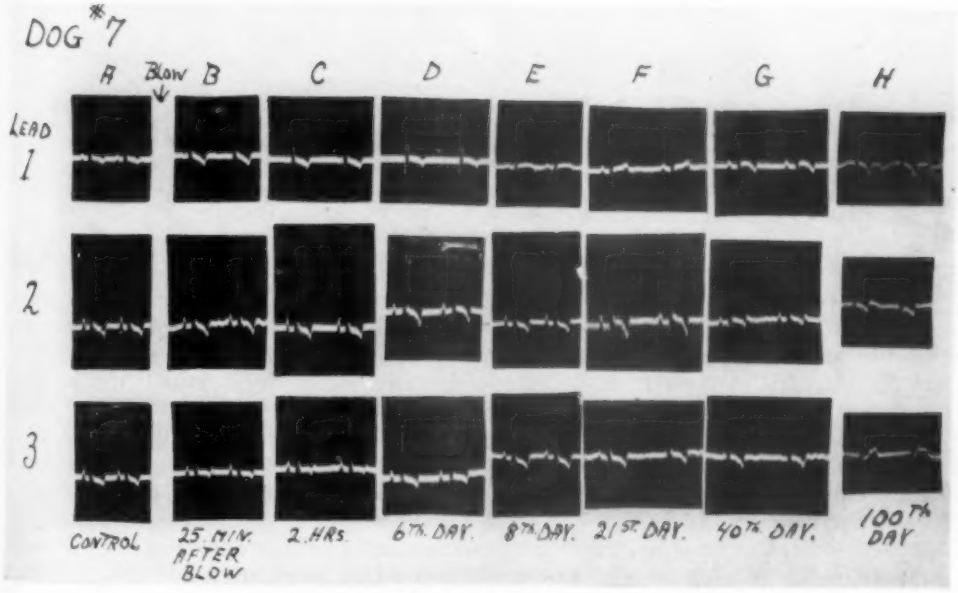

FIG. 10. Dog 7.

was performed. Gross and microscopic examinations did not reveal abnormal lesions.

Dog 11 (figure 15). A mongrel bitch, weight 17 pounds, was given 0.5 gm. sodium amytal intraperitoneally, and one hour later control electrocardiogram *A* was taken. Immediately afterwards one hard blow was struck with a five pound hammer on the area of maximum intensity of the apex beat on the left chest wall. Following this blow electrocardiogram *B* was taken in two minutes, *C* in three minutes, *D* in four minutes, *E* in six minutes (figure 16), *F* in eight minutes, *G* in 11 minutes, *H* in 14 minutes, and *I* in 21 minutes (figure 17), at which time the animal died. An autopsy was performed, but gross and microscopic examinations failed to reveal any abnormal lesions.

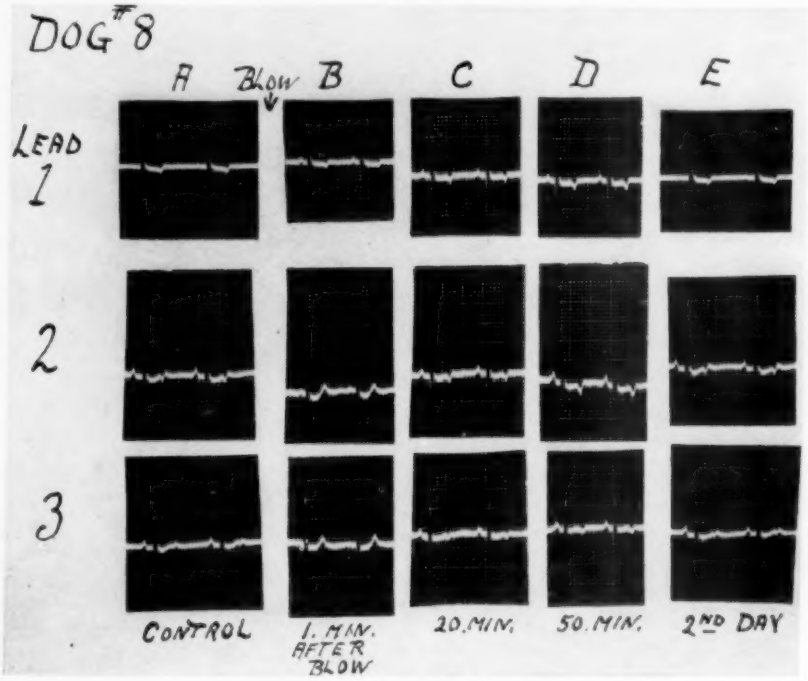

FIG. 11. Dog 8.

Dog 12 (figure 18). A short-haired mongrel bitch, weight 15 pounds, was given 0.5 gm. of sodium amytal intraperitoneally and one hour later the control electrocardiogram *A* was taken. One heavy blow with a 10 pound hammer was delivered to the left chest of the animal, and one minute later electrocardiogram *B* was taken, and four minutes later electrocardiogram *C* was taken. At this time another blow of the same type was struck (figure 19), and in one minute electrocardiogram *D* and in nine minutes electrocardiogram *E* were taken. A similar blow was again delivered, and following this electrocardiogram *F* was taken in one minute, *G* in three minutes, and (figure 20) *H* in 13 minutes. Again a similar blow was delivered and following this electrocardiogram *I* was taken in one minute and *J* in four minutes at which time the animal died. An autopsy was performed which revealed free blood in both pleural cavities, hemorrhage in the anterior and posterior mediastinal spaces, contusion of the entire right lung with a small marginal rupture of both this and the left

lung. There was hemorrhage about the base of the heart and a three inch rupture in the parietal pericardium anteriorly where it joins the great vessels, with a small amount of free hemorrhage in the pericardial sac. There was an area of contusion one inch in diameter, with hemorrhage in the anterior wall of the right auricle close to the superior vena cava. Microscopic examination revealed slight hemorrhage beneath the visceral pericardium of the right auricular myocardium and moderate hemorrhage of the lungs.

Dog 13 (figure 21). A short-haired mongrel dog, weight 25 pounds, was given 0.75 gm. sodium amytal intraperitoneally, and one hour later the control electro-

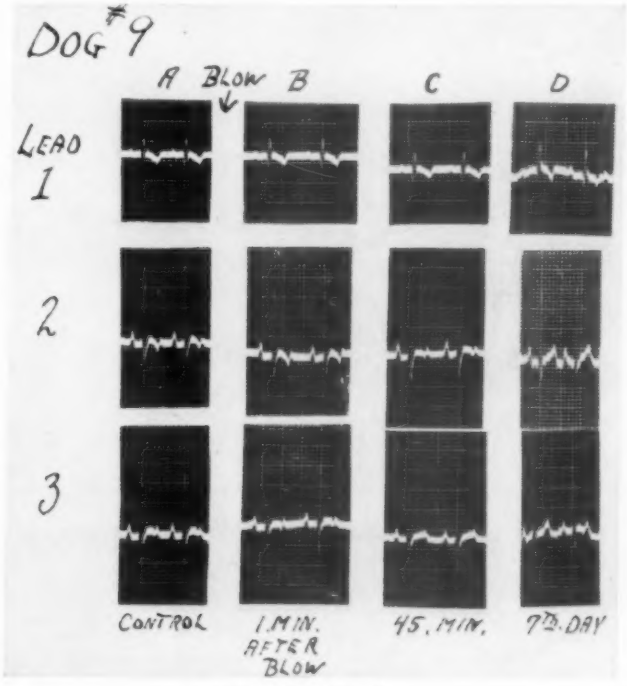

FIG. 12. Dog 9.

cardiogram *A* was taken. Then while electrocardiogram *B* was being taken one hard blow was struck with a 10 pound hammer to the left chest of the animal. Following this (figure 22) electrocardiogram *C* was taken in one minute, *D* in four minutes, *E* in five minutes, *F* in eight minutes, and *G* in 11 minutes at which time the dog died. An autopsy was performed which revealed hemorrhage into the anterior and posterior mediastinal spaces, hemorrhage into the tissue about the great vessels; also small areas of contusion and hemorrhage into the myocardium of the anterior wall of the right and left auricles. There was a small amount of free blood in the pericardial sac. Microscopic examination revealed a small amount of hemorrhage under the visceral pericardium of the right and left auricular myocardium.

Dog 14 (figure 23). A German Shepherd dog, weight 70 pounds, was given 1.5 gm. of sodium amytal intraperitoneally, and one hour later control electrocardiogram *A* was taken, following which the right and left vagus nerves and the superior and middle cervical ganglions were cut on both sides, and the spinal cord severed between the third and fourth cervical vertebrae, and after this was accomplished the

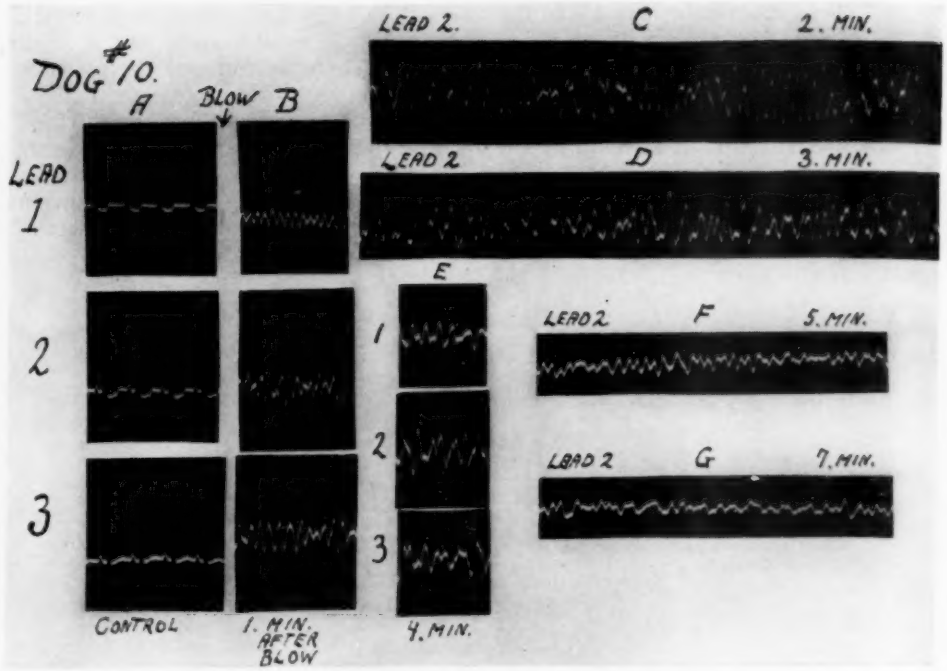

FIG. 13. Dog 10.

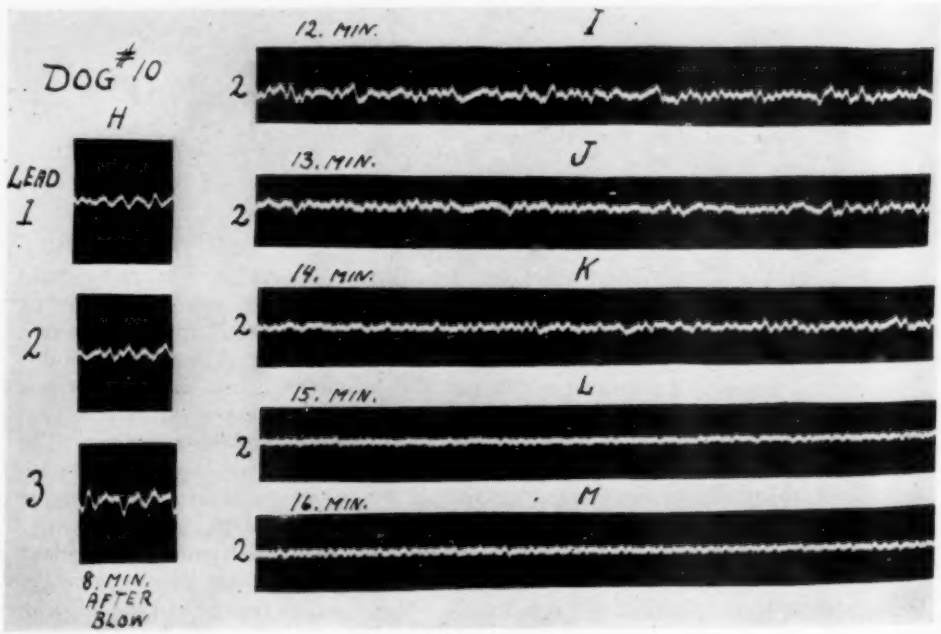

FIG. 14. Dog 10.

control electrocardiogram *B* was taken. While electrocardiogram *C* was being taken a hard blow was struck with a five pound hammer directly to the left chest at the point of maximum intensity of the apex beat. Five minutes later while electrocardiogram *D* was being taken the same type of blow was again delivered, and the same procedure repeated in five more minutes while electrocardiogram *D* was being

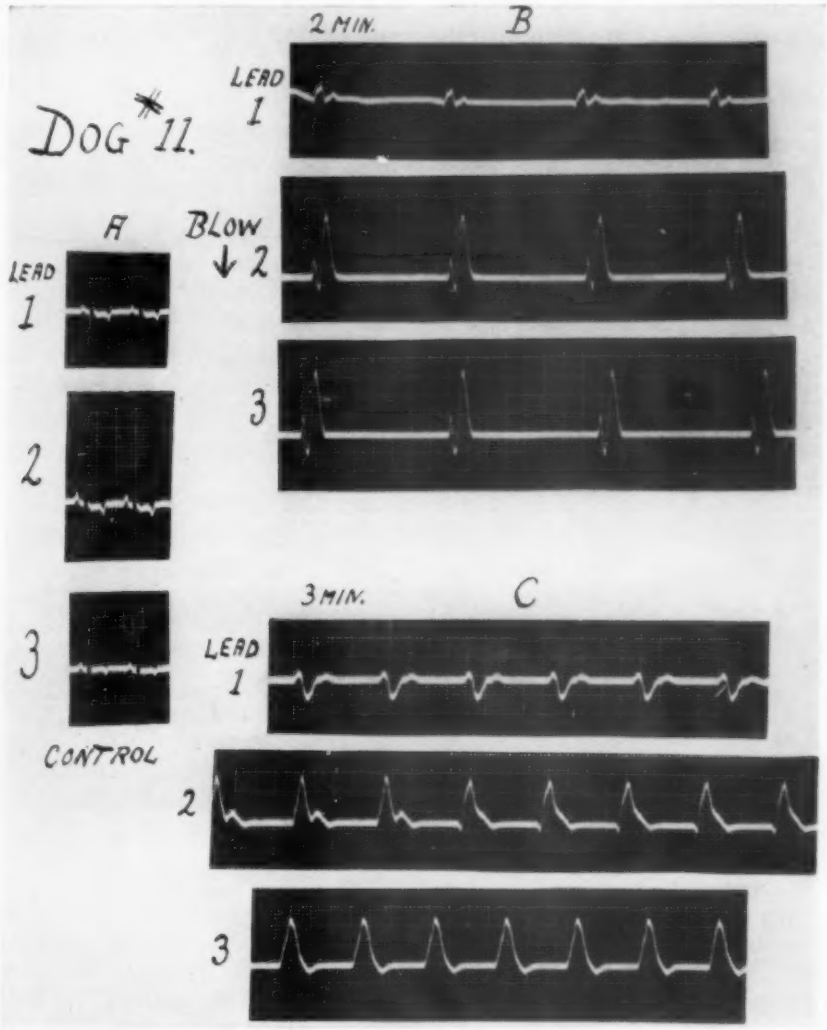

FIG. 15. Dog 11.

taken. Thirty-one seconds after electrocardiogram *D* the electrocardiogram *F* (figure 24) was taken, and five minutes after the previous blow another similar one was delivered while electrocardiogram *G* was being taken, followed in one minute by electrocardiogram *H*. Five minutes after the previous blow another similar blow was delivered while electrocardiogram *I* was being taken. Five minutes later this procedure was repeated while electrocardiogram *J* (figure 25) was being taken.

Three seconds later electrocardiogram *K* was taken, two minutes *L*, four minutes *M*, and six minutes later electrocardiogram *N*. Five minutes after this last electrocardiogram another similar blow was struck while the electrocardiogram *O* (figure 26) was being taken, and one minute later electrocardiogram *P* was taken. After a five minute interval another similar blow was struck while electrocardiogram *Q* was being taken and the tracings *R* and *S* (figure 27) are continuous with the previous electrocardiogram. *T* was taken three seconds later and *U* 42 seconds after this. Five minutes after this last electrocardiogram another blow of the same type

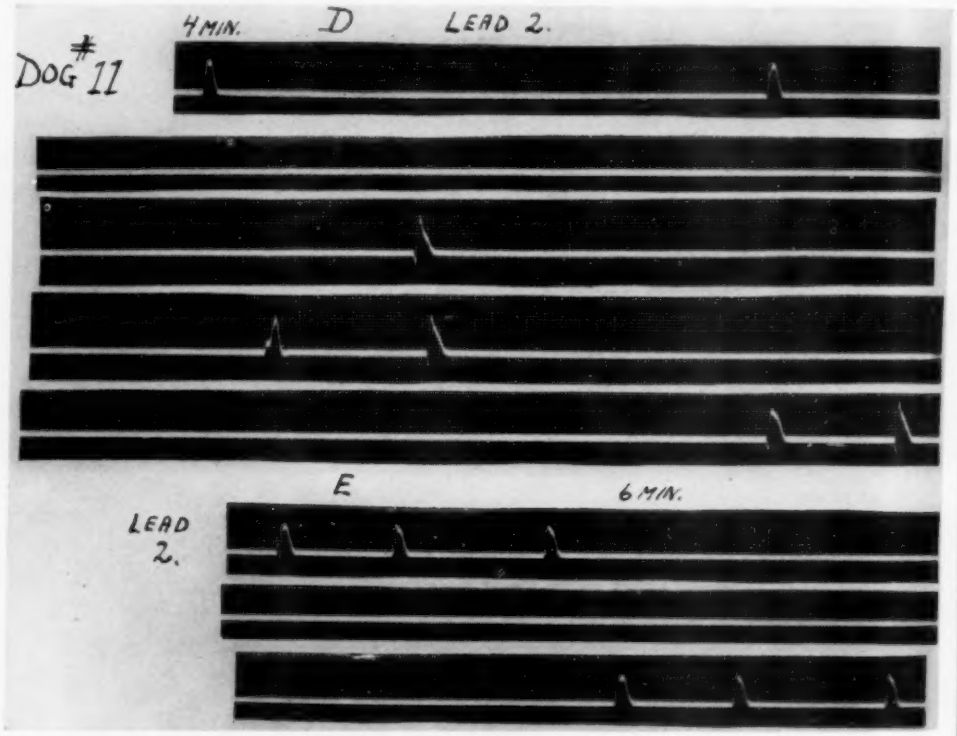

FIG. 16. Dog 11.

was delivered while electrocardiogram *V* was being taken, and the procedure repeated in five more minutes while electrocardiogram *X* (figure 28) was being taken. Electrocardiogram *W* was continuous, and then again the blow was repeated, while electrocardiogram *Y* was being taken. At this time the dog was killed by chloroform and an autopsy performed which showed that the right and left vagus nerves had been cut, as well as the superior and middle cervical ganglions on both sides and the spinal cord. There was a small amount of ecchymosis into the intercostal muscles of the third and fourth left interspaces just to the left of the sternal margin, and the second and third ribs on the right were fractured without displacement at the costochondral junction. Corresponding to these external injuries were small areas of ecchymosis in the pleura. There was a moderate amount of hemorrhage in the extreme apical portion of both lungs. The pericardial sac contained about two ounces of clear fluid and on the anterior visceral pericardium near the apex was a small roughened opaque area two cm. in diameter, while just to the left of this was a

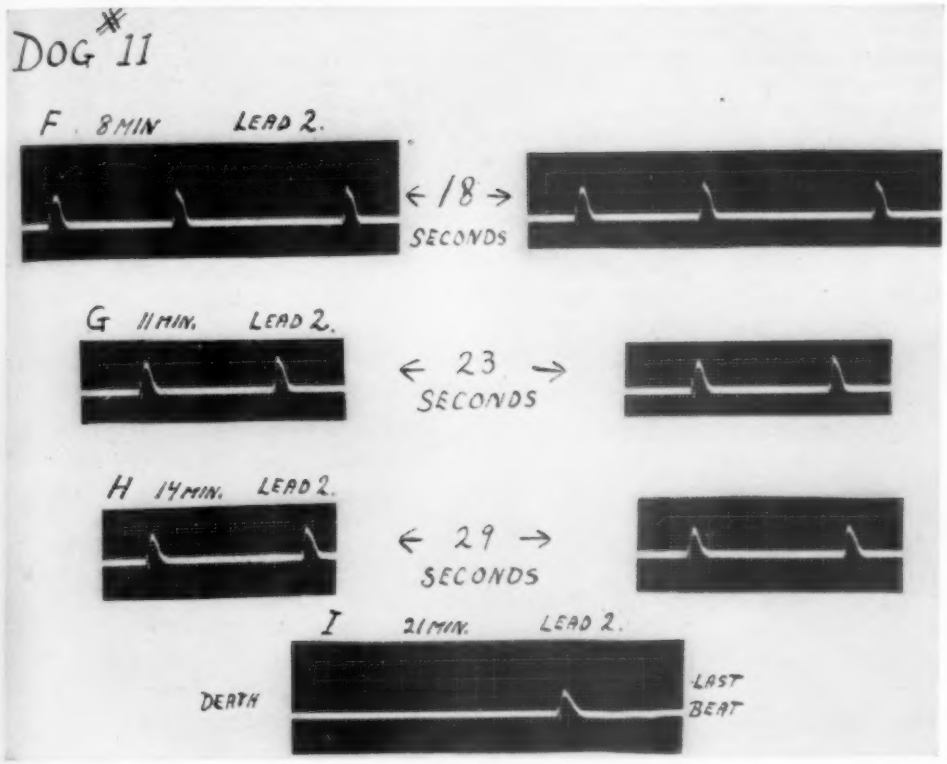

FIG. 17. Dog 11.

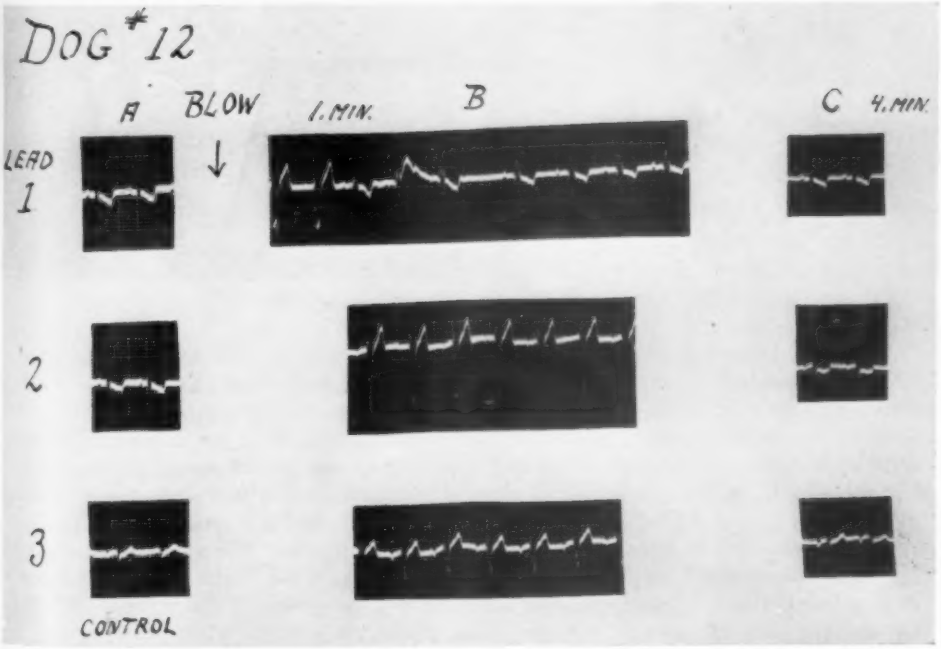

FIG. 18. Dog 12.

small area of hemorrhage and muscle contusion. There was a small rupture 6 mm. in length between the anterior cusp and the right posterior cusp of the aortic valve with moderate hemorrhagic infiltration about the base of this valve but no invasion of the myocardium. Microscopic examination revealed the hemorrhages of the anterior wall and the septal portion of the left ventricle to be limited to the subendothelial tissue and not to invade the myocardium. Sections taken through the area of pericardial thickening on the anterior surface of the left ventricle revealed an old pericardial scar consisting of fibrous tissue which in some areas was piled up in a villus like manner. The lungs showed extensive hemorrhagic infiltration of the interstitial tissue and the alveoli and a moderate amount of atelectasis.

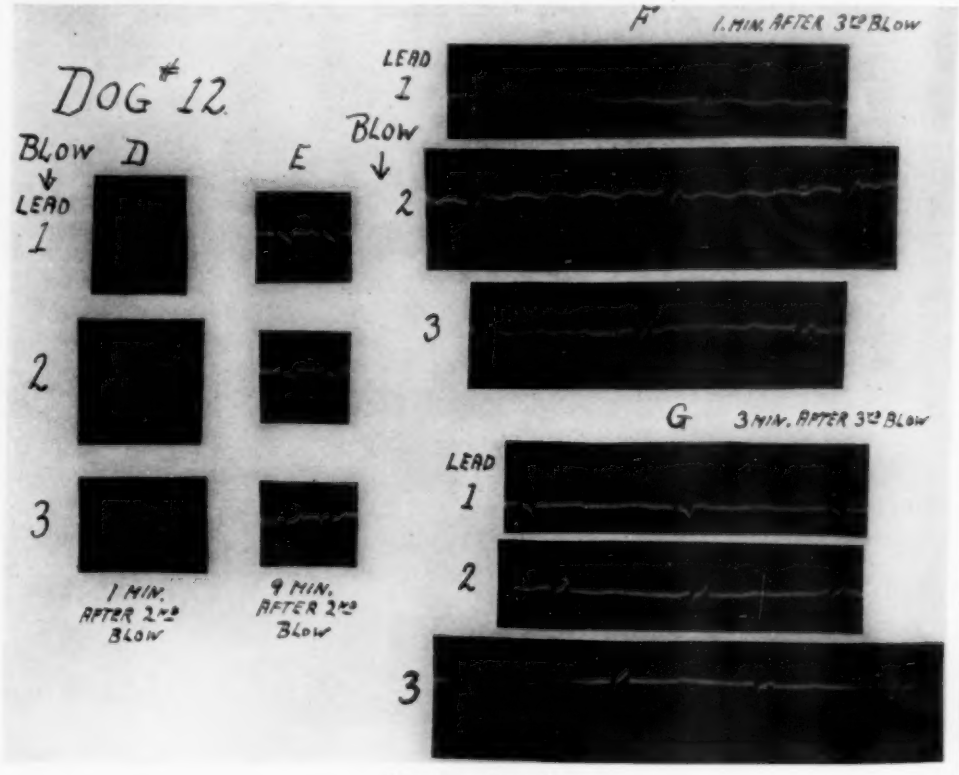

FIG. 19. Dog 12.

Dog 15 (figure 29). A mongrel English setter, weight 35 pounds, was given 0.75 gm. of sodium amytal intraperitoneally, and one hour later the control electrocardiogram *A* was taken. At this time both vagus nerves, the superior and middle cervical ganglions on both sides, and the spinal cord between the third and fourth cervical vertebrae were cut. Following this control electrocardiogram *B* was taken, and then while electrocardiogram *C* was being taken a hard blow was struck with a five pound hammer to the area of maximum intensity of the apex beat on the left chest wall, one minute later electrocardiogram *D* was taken. Then five minutes after this electrocardiogram another similar blow was delivered while the electrocardiogram *E* was being taken, and one minute later electrocardiogram *F* was taken. After a five-minute interval another similar blow was struck while electrocardiogram *G*

(figure 30) was being taken, and again the procedure was repeated after a five-minute interval while electrocardiogram *H* was being taken and electrocardiogram *I* starts 62⅖ seconds after *H*, and is continued on electrocardiogram *J* (figure 31). The electrocardiograms follow each other after various time intervals; *K* after 15⅘ seconds, *L* one minute later, *M* (figure 32) 13⅗ seconds later, *N* two minutes later, *O* three minutes later, *P* two minutes later, and *Q* two and one-half minutes later, at which time the dog died. An autopsy showed that the right and left vagus nerves

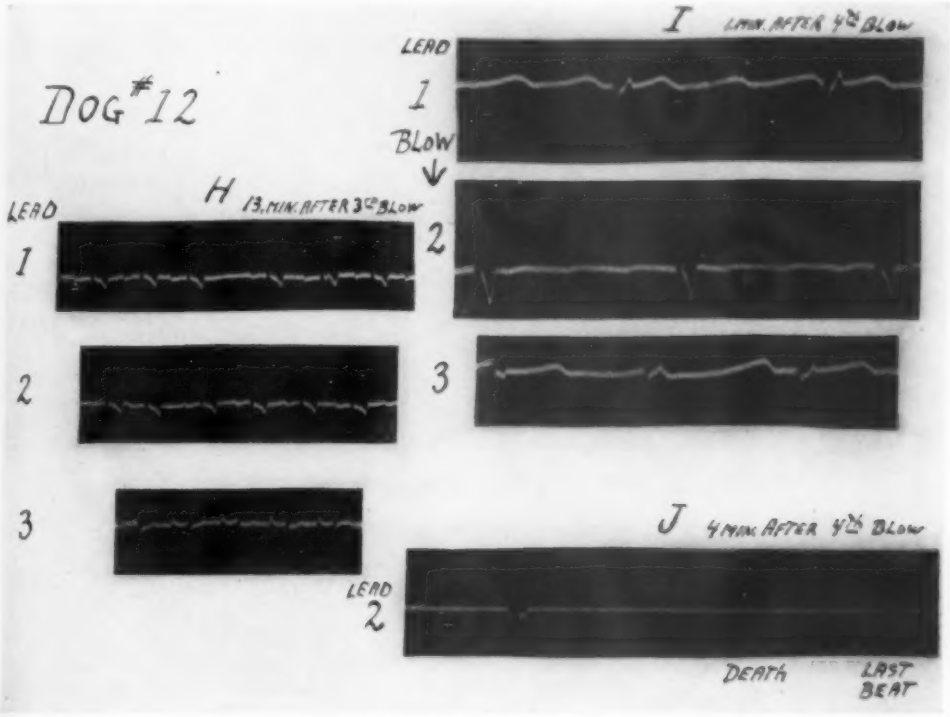

FIG. 20. Dog 12.

had been cut as well as the superior and middle cervical ganglions on both sides and the spinal cord. There was a small rent two inches long through the intercostal muscle of the left fourth intercostal space about two inches from the sternal margin with slight ecchymosis of the surrounding muscle tissue, but there were no fractures of the ribs or sternum. There was a massive collapse of both lungs with a small amount of bloody fluid into the pleural cavities. There were two tears about one cm. in length in the endocardium of the auricles, one close to the superior vena cava and the other just above the mitral valve. There was also a small rent in the superior surface of the liver. Microscopic examination revealed some atelectasis and moderate hemorrhagic infiltration of the lungs. Sections of the tears in the auricles showed a superficial absence of the endocardium which was replaced by fresh hemorrhage infiltrated slightly into the underlying muscle tissue.

General Remarks

All electrocardiograms were taken in Leads I, II and III unless otherwise stated, and all leads were standardized at the time of each electrocardiogram. The electrodes used were of the ordinary small metal type, and the position of the animal remained the same throughout each experiment, but

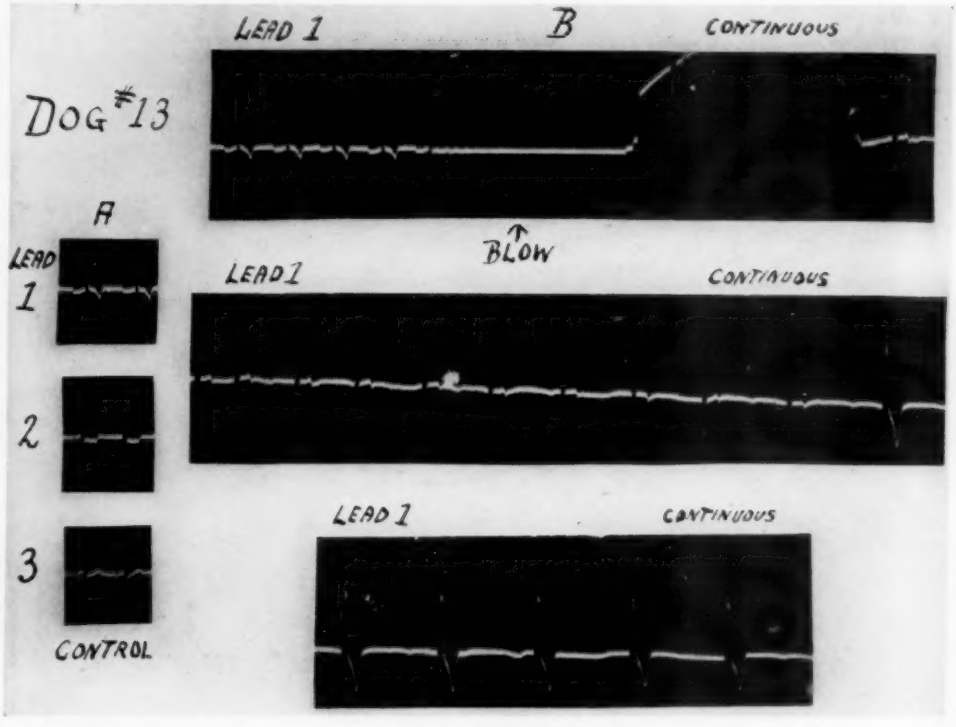

Fig. 21. Dog 13.

the animals that were allowed to recover from the anesthesia and live were taught to stand still while the electrocardiograms were taken. Many microscopic sections were studied on each animal from the pericardium, walls of the great vessels, myocardium, coronary vessels, cusps of the valves, conduction system and lungs.

Electrocardiographic Results

Dog 1 (figure 1). Five minutes after a moderate blow there was an increase in the T_1 negativity (ekg. *B*) from the control and the T_3 became positive. There was no further change until five and one-half hours after a second blow when the T_1 and T_2 became deeply inverted and the T_3 upright and pointed, with variation in the RS–T component (ekg. *G*).

Dog 2 (figure 2). The first series of moderate blows did not produce

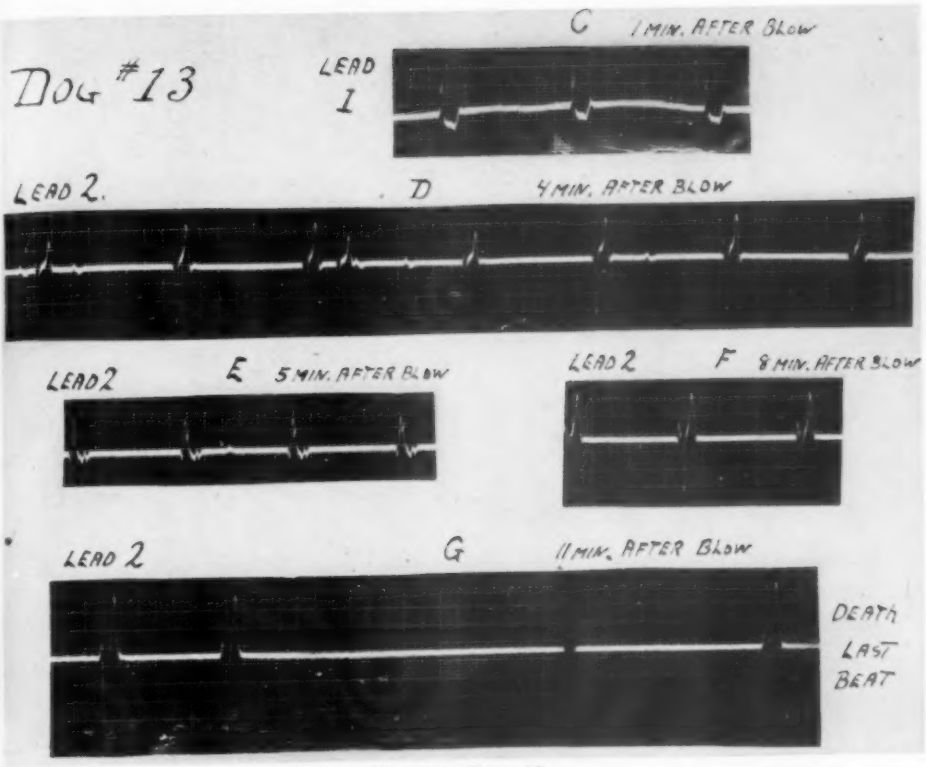

FIG. 22. Dog 13.

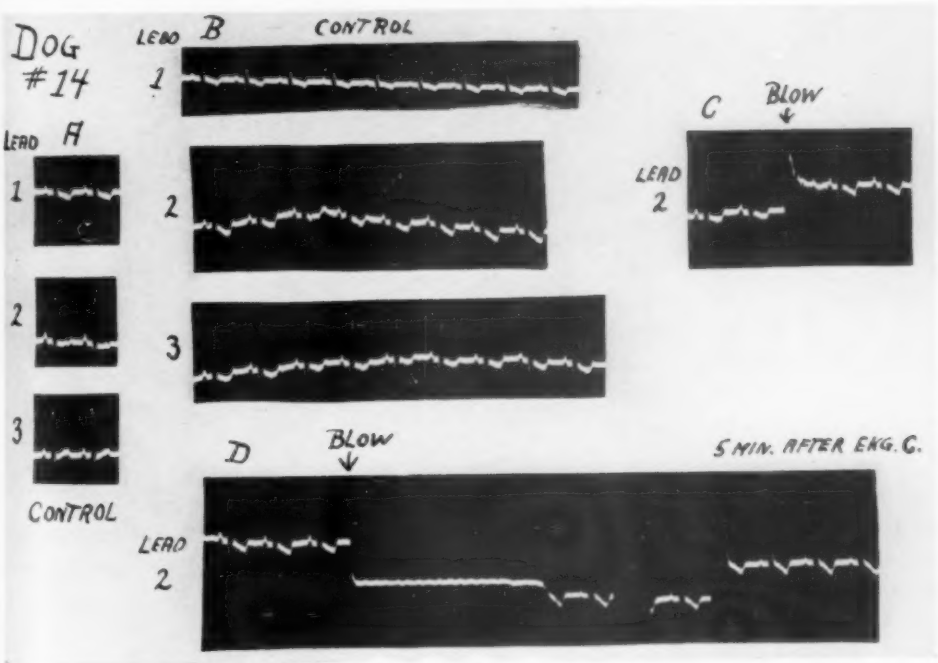

FIG. 23. Dog 14.

any marked deviation in the electrocardiogram from the control but five and three-fourths hours later and 45 minutes after the second series of blows the T_1 and T_2 changed to positive and the Q_1 disappeared (ekg. *H*).

Dog 3 (figure 3). Five minutes after the first blow (ekg. *B*) the T_3 became negative and the downward deflection of the QRS_3 in the control disappeared and became upright. These changes were not influenced by the following series of blows.

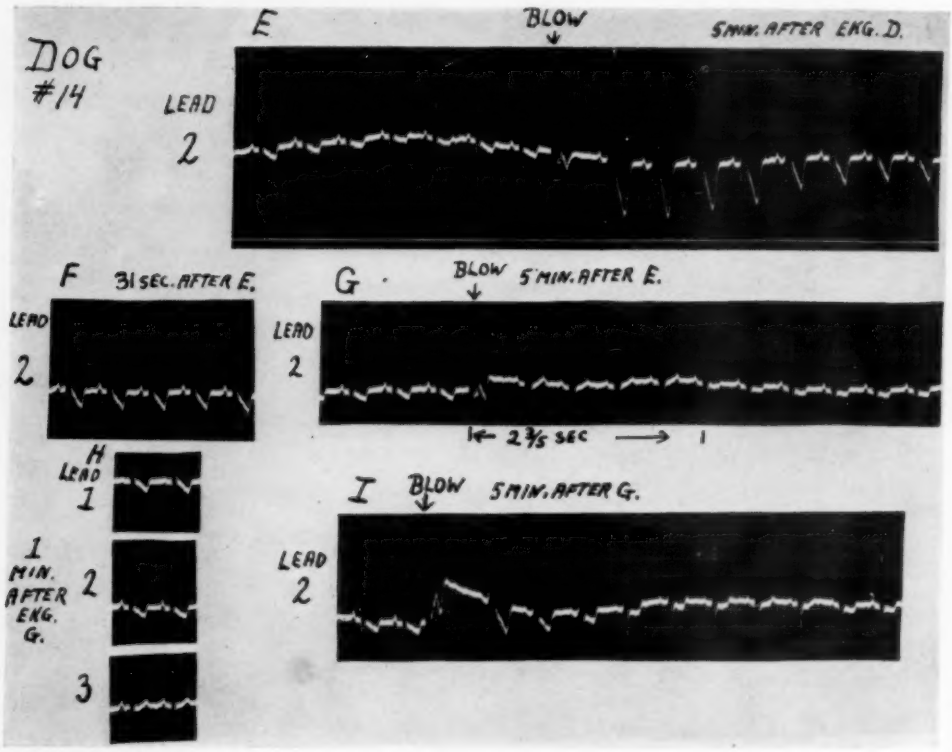

FIG. 24. Dog 14.

Dog 4 (figure 4). Five minutes following a heavy blow (ekg. *B*) there was a change from the control to a negative T_1, T_2 and T_3, and one and one-half hours later (ekg. *D*, Lead II) and two and one-half hours later (ekg. *E*, Lead III) transient sino-auricular block appeared.

Dog 5 (figure 5). Twelve seconds after a hard blow there was a change from the control in the RS–T component and (figure 5, ekg. *B*) the T_1 became negative while the T_3 changed to positive, but later returned to negative as in the control. One and one-half hours later another hard blow was struck and within 10 seconds (figure 7, ekg. *G*) interventricular block developed in Leads I and II with rapid decrease in the greatest deflection on the QRS wave and return to normal rhythm in Lead III. The

negative T_1 which occurred immediately following the first blow became more marked and was still present (figure 8, ekg. *K*) two and one-half hours after the second blow.

Dog 6 (figure 9). After four series of heavy blows there were no marked electrocardiographic changes.

Dog 7 (figure 10). After a heavy blow was delivered there were no marked electrocardiographic changes until the eighth day when the T_1 be-

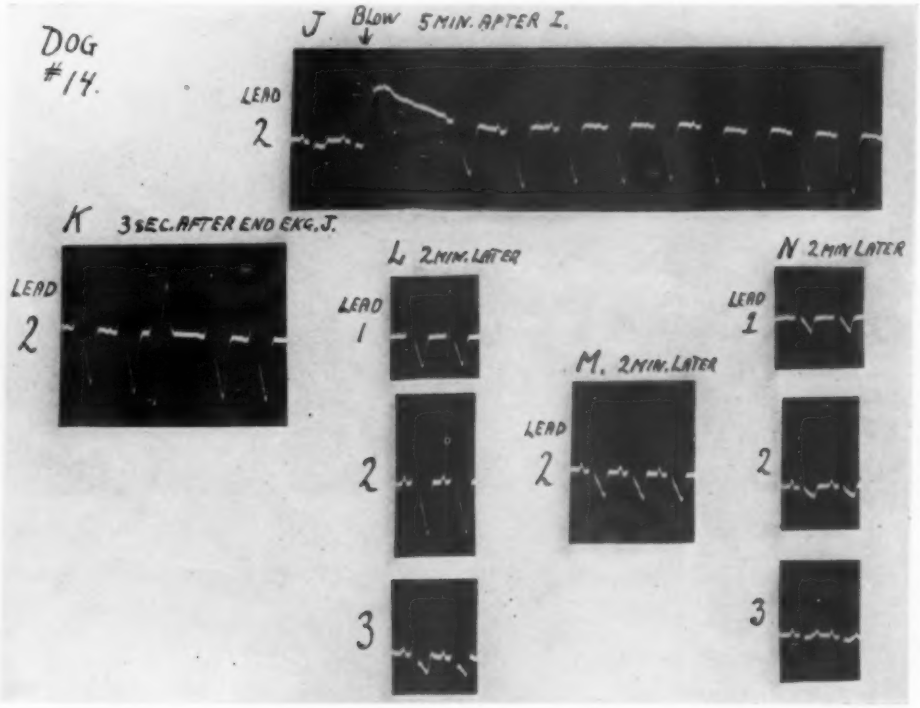

FIG. 25. Dog 14.

came positive (ekg. *E*) and returned to negative on the fortieth day (ekg. *F*) and at this time what appeared to be ventricular extrasystoles were seen by the string shadow but were not caught by the camera. The T-wave became positive in Lead II on the hundredth day (ekg. *H*). There was also marked deviation of the RS–T component in the electrocardiograms taken after the eighth day (ekg. *E, F, G, H*), and on the hundredth day (ekg. *H*) no P-wave was seen in Leads II and III and in Lead I there appears to be a diphasic P-wave with a P–R interval of 0.24 second.

Dog 8 (figure 11). One minute after a hard blow (ekg. *B*) there was a change from the control to a positive T_2 and T_3 but this was transient and on the second day (ekg. *E*) the electrocardiogram was similar to the control.

Dog 9 (figure 12). There were no marked changes from the control

in the electrocardiograms taken following the blow until the seventh day (ekg. *D*) when the T_2 and T_3 were positive.

Dog 10 (figure 13). One minute after the blow the electrocardiogram *B* revealed ventricular fibrillation which ended in death 16 minutes later (figure 14, ekg. *M*).

Dog 11 (figure 15). Two minutes after the blow (ekg. *B*) there is an absence of the P-wave, evidently an auricular paralysis with an idio-ventricular rhythm. Three minutes after the blow (ekg. *C*) there is an idio-

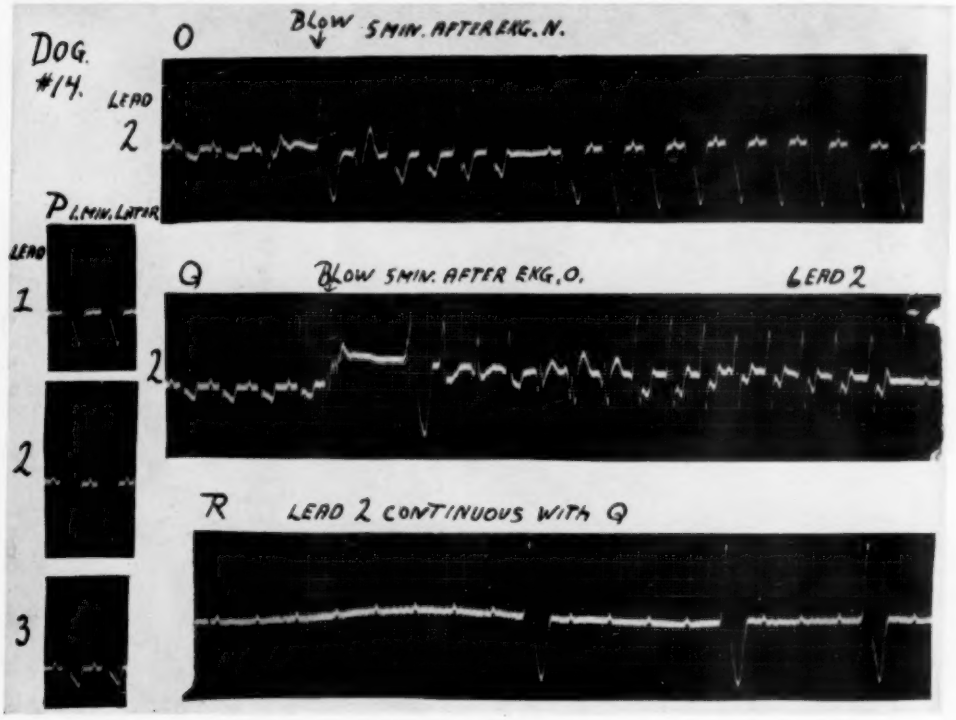

FIG. 26. Dog 14.

ventricular rhythm and in Lead I the P-wave appears following the QRS wave, and also in the first part of Lead II, and in the fourth complex the P-wave begins to be gradually incorporated in the QRS wave until the P-wave has completely disappeared and permanent auricular paralysis established with monophasic ventricular complexes of the dying heart (figure 16, ekg. *D, E*). Death occurred 21 minutes after the blow (figure 17, ekg. *I*).

Dog 12 (figure 18). One minute after a blow the electrocardiogram changed from the control to (ekg. *B*) an interventricular block, which in Lead I is shown to be transient and suddenly in the third complex the QRS wave greatly decreases in magnitude and the T-wave becomes inverted until in four minutes the complexes in all leads (ekg. *C*) have returned to

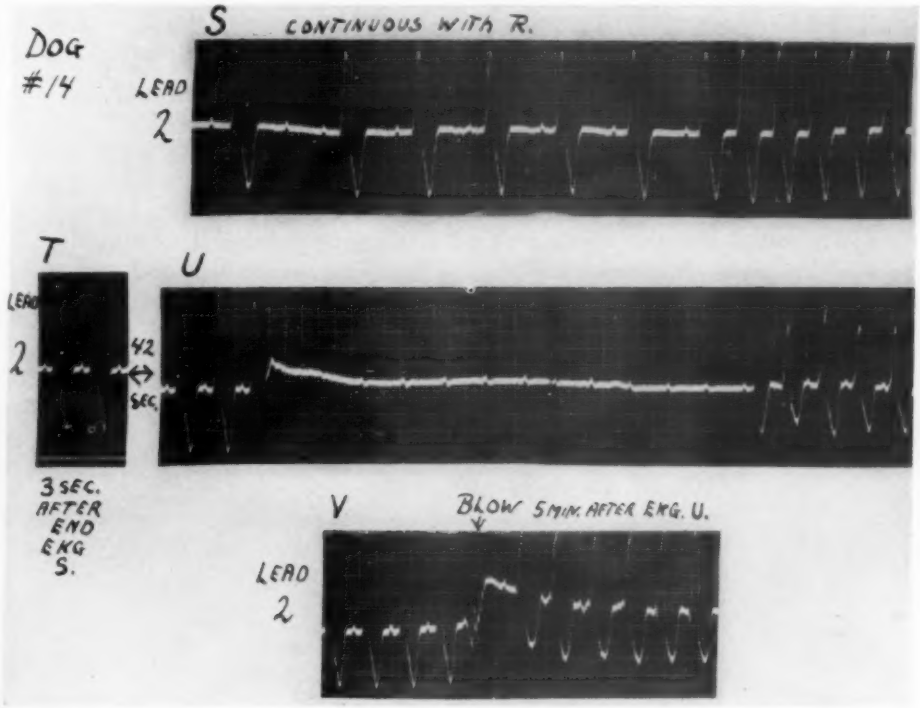

FIG. 27. Dog 14.

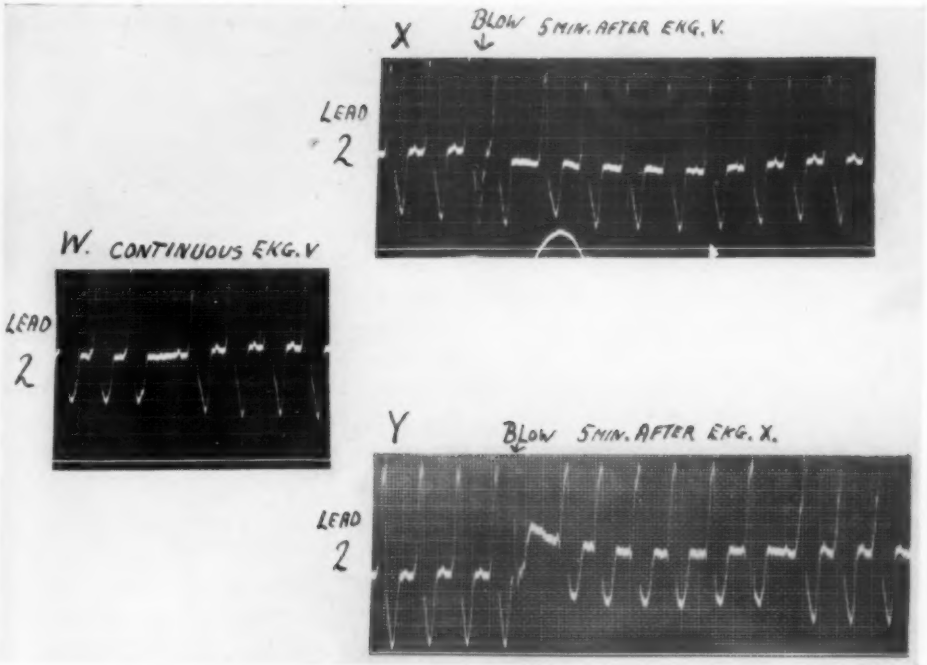

FIG. 28. Dog 14.

the type seen in the control (ekg. *A*). Another blow was struck and again within one minute (figure 19, ekg. *D*) interventricular block occurred and in nine minutes returned to the normal rhythm (ekg. *E*) seen in the control. Another blow was struck and one minute later (ekg. *F*) an idio-ventricular rhythm was established with an absence of the P-wave, with slow undulating waves of the base line. Three minutes after the blow (ekg. *G*) the idio-ventricular rhythm was still present with some changes in the character of the QRS waves and the appearance of a negative pointed T_1 wave. Thir-

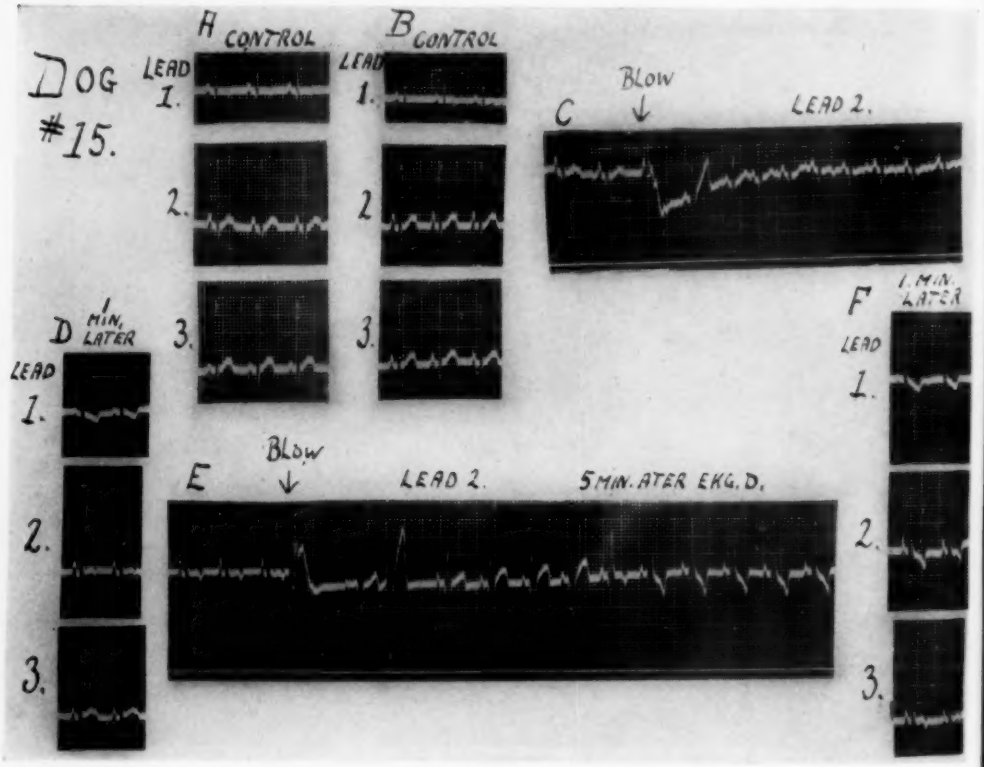

FIG. 29. Dog 15.

teen minutes after this blow (figure 20, ekg. *H*) there was a return to the normal rhythm of the control and sino-auricular block in Lead I. One minute after another blow (ekg. *I*) idio-ventricular rhythm appeared with no P-waves and slow rhythmic undulations of the base line and after four minutes there was (ekg. *J*) auricular paralysis with monophasic ventricular complexes and death at this time.

Dog 13 (figure 21). While Lead I of the electrocardiogram was being taken (ekg. *B*) a blow was delivered with the string protected and in 4.2 seconds interventricular block with gradual slowing of the rate until, in 12.6 seconds all signs of a P-wave disappeared with an idio-ventricular

rhythm. One minute after the blow (figure 22, ekg. *C*) the rhythm was the same but the ventricular complexes changed in character and after four minutes (ekg. *D*) there was a complete heart block with idio-ventricular rhythm, an occasional ventricular extrasystole, and pairs of rhythmic P-waves separated by long intervals of auricular paralysis and idio-ventricular rhythm with diphasic ventricular complexes until death in eleven minutes (ekg. *E, F, G*).

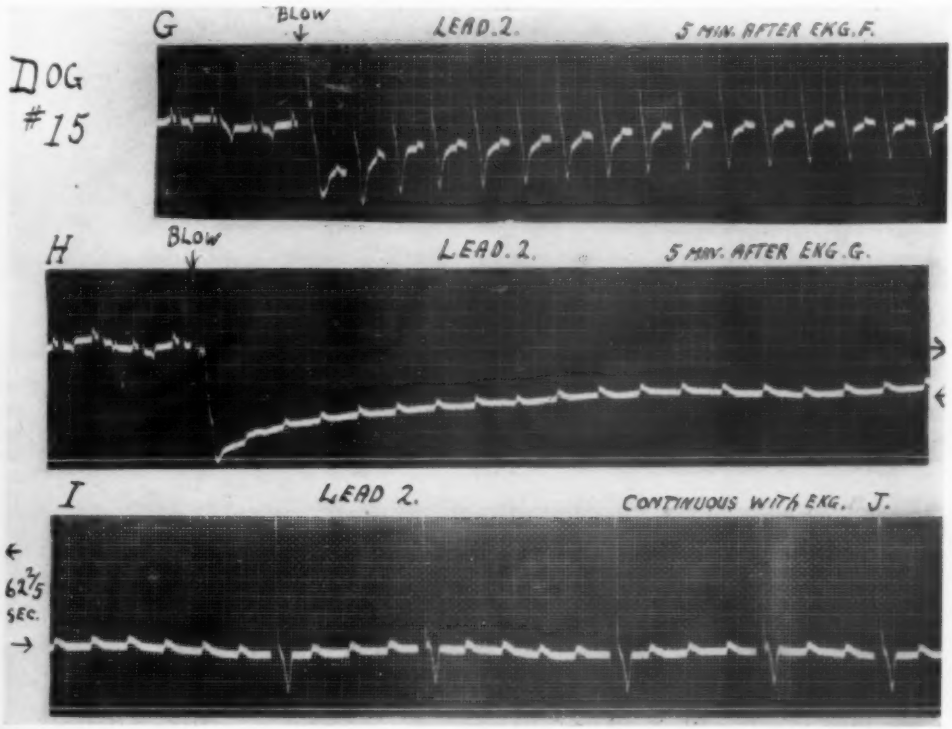

FIG. 30. Dog 15.

Dog 14 (figure 23). Two blows were delivered while Lead II of the electrocardiogram was being recorded (ekg. *C, D*) without marked changes. The blow was repeated (figure 24, ekg. *E*) in the same manner and in 0.6 second and with the next complex, interventricular block occurred which was transient and (ekg. *E, F*) returned to the normal rhythm (ekg. *G*) of the controls in five minutes. At this time another blow was struck while Lead II of the electrocardiogram was being taken (ekg. *G*). The next beat after the blow revealed a change to an upright T-wave, change in the RS–T component and the Q-wave of the QRS complex disappeared and the initial deflection of the ventricular complex became upright. These changes were transient and within 2.6 seconds the QRS wave returned to the former character and the T-wave became negative. One minute later (ekg. *H*)

there was a return to the normal rhythm of the controls. Five minutes later (ekg. *I*) the blow was repeated while Lead II of the electrocardiogram was being taken and the next complex revealed a transient interventricular block with return to the control rhythm in three seconds. Five minutes later another blow was struck (figure 25, ekg. *J*) while Lead II of the electrocardiogram was being taken and after 0.8 second of cardiac standstill interventricular block developed, with an occasional ventricular extrasystole (ekg. *K*), which was transient (ekg. *K*, *L*, *M*, *N*) and returned to the nor-

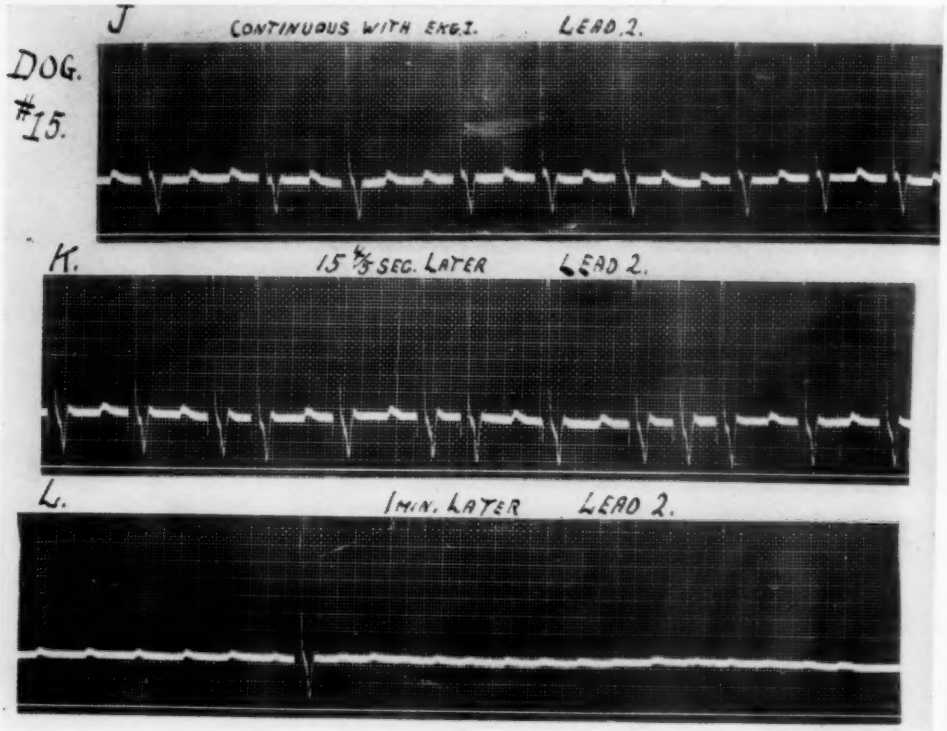

FIG. 31. Dog 15.

mal control rhythm (figure 26, ekg. *O*) 11 minutes after the blow, at which time the blow was repeated under like circumstances (ekg. *O*). Immediately ventricular tachycardia developed and in 2.2 seconds a P-wave appeared with interventricular block (ekg. *P*). Then after another five-minute interval another similar blow was struck (ekg. *Q*) which was followed by 0.8 second of cardiac standstill, then by ventricular tachycardia with various types of diphasic ventricular complexes, and after 6.8 seconds a P-wave appeared with a complete heart block and only occasional idioventricular complex (ekg. *Q*, *R*) which became more frequent until, after six seconds (figure 27, ekg. *S*) there is 2 to 1 block and in seven seconds interventricular block, changing in 10.4 seconds to ventricular tachycardia,

then back to interventricular block (ekg. *T*). About 42 seconds later there was complete heart block with ventricular standstill followed by interventricular block again (ekg. *U*). Five minutes later another blow was delivered while (ekg. *V*) the interventricular block was present without marked changes. Five minutes later when this was repeated (figure 28, ekg. *X*) the interventricular block disappeared and ventricular tachycardia occurred for five complexes, after which there was a return to interventricular block, with occasional changing back and forth between these rhythms (ekg. *W*, *Y*).

Dog 15 (figure 29). A blow was delivered while Lead II of the electrocardiogram was being taken (ekg. *C*), which was followed by one ventricular extrasystole with immediate return to the normal control rhythm (ekg. *C*, *D*). This was repeated five minutes later with transient interventricular block of the right and left branches of the Bundle of His and one ventricular extrasystole, each change being separated from the other by a normal complex (ekg. *E*) and in one minute the rhythm of the control returned (ekg. *F*). After another five-minute interval a similar blow was given and again (figure 30, ekg. *G*) transient interventricular block immediately developed to return to the normal control rhythm in five minutes when the final blow was delivered, followed by complete heart block and ventricular standstill for 73 seconds (ekg. *H*, *I*) after which 5 to 1, 4 to 1, 3 to 1, and 2 to 1 block occurred (figure 31, ekg. *J*). The idio-ventricular complexes appear in groups of two's and three's and one minute later the P-waves became very small in amplitude (ekg. *L*), finally disappearing with one last diphasic idio-ventricular complex, then death.

Discussion and Comment

The most frequent electrocardiographic changes were in the T-waves and the RS–T components and occurred in 10 of the dogs.* In the first series of experiments with Dogs 1, 2, 3, 4 and 5, these changes occurred during a period varying from a few minutes to a few hours, after various degrees and types of chest injuries. Since all the electrocardiograms were taken with the dogs in the same position, the chance of error was removed. Only two of these five dogs showed abnormal lesions of the heart, Dog 1 with hemorrhage into the mediastinal space and cusps of the pulmonic and mitral valves and Dog 5 with thickening and hemorrhage into the pericardium and into the tissue about the base of the heart. While three of the dogs had hemorrhage into the lung, two others with more marked T-wave and RS–T component changes did not show this lesion and therefore these changes were not attributed to generalized anoxemia; neither can they be attributed to increase of the fluid in the pericardial sac because in none of the five dogs was this found to be present. The gross and microscopic examina-

* Since this article has been written additional experiments of the same type have been performed and in one dog, we were able to produce auricular fibrillation following external trauma to the chest.

tion of the hearts of these dogs revealed them to be normal except for slight hemorrhage into the valve cusps of Dog 1. In Dog 4 there were no abnormal lesions found.

The second series, Dogs 6, 7, 8 and 9, were not killed following the external chest injury. Dog 6 lived a few hours, then died from hemorrhage into both lungs. The autopsy revealed a rupture of the diaphragm and a tear in the pericardium with a small amount of hemorrhage into the pericardial sac, but there were no electrocardiographic changes observed.

Dog 7 was disregarded because following sudden death, upon the one hundred and twenty-first day, there was found some thickening of the coronary artery which was not traumatic but could possibly have caused electrocardiographic changes.

Dog 8 showed immediate T-wave and RS–T component changes, as did also Dog 9 on the seventh day. Dog 8 died on the third day and the autopsy revealed a small tear in the pericardium. Dog 9 died on the sixteenth day and the autopsy revealed congestion of the lungs and heart failure cells. Evidently in Dog 9 heart failure had been present before death, although in neither case were any abnormal lesions found in the myocardium, and it is possible that this failure may have been due to some serious type of arrhythmia which was not present at the time the electrocardiograms were taken.

The third series, Dogs 10, 11, 12 and 13, were struck heavy blows to the chest in an attempt to produce death in as short a time as possible. In Dog 10 ventricular fibrillation was produced with death in sixteen minutes; in Dog 11 idio-ventricular rhythm with auricular paralysis occurred with death in 21 minutes. The autopsies failed to reveal any abnormal lesions. Dog 13 had immediate changes in the T and QRS waves and the RS–T component and later developed a heart block, interventricular block, and finally auricular paralysis with idio-ventricular rhythm which eventually caused death. The autopsy in this case revealed hemorrhage into the tissue about the base of the heart, into the pericardial sac with slight sub-pericardial and myocardial hemorrhage of the wall of the right and left auricles. These three dogs in the third series died as a result of fatal arrhythmias and demonstrated the possibilities of sudden death from external chest injuries with insufficient pathology to explain these arrhythmias or to be considered as a cause of death. Dogs 12, 14 and 15 demonstrated that many various types of arrhythmias occur immediately and in a very short time return to normal rhythm but with each successive chest injury the arrhythmia remained for an increasing period.

In the fourth series, Dogs 14 and 15, the right and left vagus nerves, the right and left superior and middle cervical ganglions and the spinal cord were cut before any of the blows were delivered. This was done to avoid the possibility of extra-cardiac lesions producing the electrocardiographic changes. Although the first two hard blows struck Dog 14 did not pro-

duce electrocardiographic changes, almost all the arrhythmias, T-wave and RS–T component changes seen in the other dogs were reproduced in these two animals. Similar traumatic lesions outside the heart, such as contusion and hemorrhage of the lungs, rupture of the liver and diaphragm, were produced in these dogs which would seem to indicate that the changes seen in the dogs of the other series were not due to injury outside the heart.

Considering the entire 15 animals the most frequent lesion produced was injury of some type to the lung. This occurred in eight dogs, following both severe and mild blows to the chest. Rupture of the liver occurred twice, and rupture of the diaphragm once. These lesions, together with hemorrhage into the mediastinal space, were the chief lesions found outside the heart. The most frequent cardiac lesions were sub-endocardial and sub-pericardial hemorrhage which occurred four times, as did also pericardial injury and tear with or without free blood in the pericardial sac. With the exception of hemorrhage into the valve cusps, which occurred twice, and hemorrhage into the tissue about the base of the heart, no other lesions were found. In three dogs there were no lesions of any kind and, since the electrocardiographic changes are sudden and transient, these changes may be considered due to edema of the myocardium and the various parts of the conduction system. These changes are also similar to those following experimental coronary artery occlusion and injury to the Bundle of His, in dogs. It is evident that mild and severe blows produce various types and degrees of electrocardiographic changes and the tendency is for the heart to return to normal within a very short time. On the other hand the same degree of blow may produce a fatal arrhythmia. It is also evident that there need be no injury to the chest wall, which occurred only in the two dogs of the last series, to produce both electrocardiographic changes and abnormal lesions of a serious nature.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

ADRENAL CORTICAL TUMOR; A REPORT OF FOUR CASES *

By CHARLES H. LAWRENCE, M.D., F.A.C.P., *Boston, Massachusetts*

IN his paper on tumors of the suprarenal cortex read before the Staff of the Mayo Clinic in 1933, Kepler [1] cites the following quotation from Rowntree and Ball:

"We may say that there are various types of tumors of the suprarenal gland, resulting in a large variety of clinical symptoms and syndromes, many of which are difficult to explain adequately in the present state of knowledge. Correlated clinical, pathological and chemical studies are urgently needed." The following four case reports, which more or less imperfectly meet these specifications, seem worth adding to the literature.

Case 1. F. R., female, 13 yrs. 10 mos.; first seen November 1, 1928.

Family History: Father, mother, two sisters living and well. No family history of endocrine disease. Mother's catamenia irregular and profuse. One sister hypomenorrheic through adolescence, normal since.

Past History: Measles, mumps, chicken pox, pertussis in childhood. Tonsillectomy in childhood. Appendectomy at 11 for acute appendicitis.

Present Illness: Menarche at 10 yrs. 8 months. During the next nine months menstruation was regular every 28 days, lasted four to five days, amount regarded as normal, no pain. In June 1926, patient menstruated normally but had not menstruated since, an interval of 17 months. During the first six months of amenorrhea there was no change in her general condition, and little attention was paid to the lack of menstruation.

In June 1927, patient's mother noted beginning masculinization. The voice became deeper and hoarser, and coarse dark hair appeared on arms, legs, abdomen, cheeks and chin. Both voice change and hair growth increased steadily. The patient's general health remained excellent. She denied any other symptoms than those enumerated.

Physical examination showed a well developed and nourished girl. The body contour was normally feminine. There was moderate acne of the face, chest and back. There was moderate hypertrichosis of cheeks, chin, and upper lip, and a considerable growth of coarse, dark hair on the arms and legs. The pubic hair extended upward to the navel. The labia were slightly hypoplastic, the clitoris was slightly larger than normal. Rectal examination disclosed a rather small uterus, but no other pelvic abnormality. Abdominal examination revealed no abnormality. The physical findings were otherwise normal.

Laboratory Findings: The urine was normal as was the blood morphology, and chemistry. Renal function (phenolsulphonephthalein elimination) was 59 per cent in two hours. Basal metabolism was plus 3 per cent, with normal pulse rate, blood pressure and temperature. Roentgen-rays of the skull, kidneys and urinary tract showed no pathology. Eye grounds and visual fields were normal. Pelvic ex-

* Received for publication July 28, 1937.
From the Endocrine Clinic of the Boston Dispensary.

amination with anesthesia showed no abnormality other than slight uterine hypoplasia.

Course: The sudden cessation of previously normal menstruation, and the masculinization suggested either tumor of the adrenal cortex, pineal tumor, or tumor of the ovary. (Basophilic adenoma of the pituitary was unknown at that time.) No diagnosis could be definitely established, however, and the patient was kept under observation for a year. During this period no change occurred in the clinical picture, there was no loss of weight, and the blood pressure, observed repeatedly, remained perfectly normal. Injections of "Amniotin" and "Estrogen" were without demonstrable effect.

At the end of a year, the patient was seen in consultation by Dr. D. L. Jackson, who confirmed the physical findings already noted. In his opinion, sclerosis of the ovarian cortices was the most probable diagnosis, and at the request of the patient, an exploratory operation was performed, December 5, 1929.

Operative Findings: The cervix was small. Curetting the uterus yielded no endometrium, in spite of the fact that a serrated curet was used. On opening the abdomen, the uterus was found to be small and retroverted. The Fallopian tubes were normal. The ovaries were smooth with thickened cortices. Both ovaries were split, and were found packed with small cysts, which were evacuated. The cortex was then pealed. The left kidney and adrenal body were normal to palpation. There was a question as to whether the right adrenal gland could be felt, but no pathological condition could be demonstrated. The wound was therefore closed. Pathological report on the curettings: No endometrial tissue found. Specimen from ovary—simple cyst, and numerous unripe follicles.

The patient made an uneventful recovery. There was no change in the clinical picture. She was seen at intervals of three to six months during the next six years, but no significant development occurred until September 1934 (nearly five years after operation), when she began to develop moderate dyspnea and palpitation on vigorous effort. Examination at that time showed the heart to be normal, but the resting pulse rate had increased to 96 per minute, and the blood pressure had risen to 140 systolic and 80 diastolic. The retinal arteries were slightly narrow, the veins moderately over full. Blood and urine were normal. The breasts had become atrophic, and there was marked hair growth around the areolae. Abdominal examination was negative. Intravenous pyelograms showed that the right kidney was larger than the left, and its border was somewhat irregular. The pelves, infundibulae and calices filled well, but the upper calix of the right kidney was depressed. There were no other abnormal findings. Neither Dr. Prather nor Dr. Morrison, who together conducted the examination, felt that there was enough evidence of adrenal tumor to justify operation. They advised further observation.

In April 1935, the patient's condition was essentially unchanged, the slight hypertension persisted, and abdominal palpation gave a sense of an indefinite mass in the right flank not apparently connected with the liver. Repetition of the pyelogram showed, on the right side, numerous small areas of calcification scattered between the levels of the first lumbar vertebra and the tenth rib posteriorly, and a suggestion of the rounded outline of a mass overlying the upper pole of the right kidney.

On the basis of these findings, the diagnosis of tumor of the right adrenal gland seemed established, and after consultation with Dr. Prather, it was decided to operate after preliminary radiotherapy had been completed. There was no significant change in the patient's condition up to the time of operation, July 25, 1935. At operation, a rounded, encapsulated tumor on the right adrenal 12.5 by 10 by 8 cm. was removed. It was completely encapsulated, fairly homogeneous, brown, opaque and soft. Scattered through it, particularly near the periphery, were bony spicules. Because of the size of the tumor it was necessary to remove both the right kidney and

the right adrenal gland with it. The latter showed a slight thickening of the cortex, and was otherwise normal. The kidney was normal.

The patient showed a fall in blood pressure to 100 systolic and 70 diastolic, 24 hours after operation. Eschatin was administered during the next three days, and gave a prompt response. Thereafter, the blood pressure varied between 120 and 130 mm. systolic with a diastolic of 80 mm. The patient made an uneventful recovery.

Within three weeks after operation her voice showed a definite return to the feminine timbre and within two months was completely restored to its former quality. The patient began to menstruate on September 1, and flowed four days normally, without pain. Thereafter she has continued to menstruate normally and regularly. One year after operation examination showed some gain in weight and marked regression of the hypertrichosis. A recent report states that the abnormal hair growth has now practically disappeared.

Comment

The outstanding feature of this case is the long duration of the syndrome before its cause could be identified. In November 1928, the masculinization was sufficiently impressive to leave no doubt that there was serious disturbance of endocrine function, but a rather complete diagnostic study afforded no evidence sufficient to identify the gland at fault. Such evidence as there was suggested pathology of the adrenal cortex or ovary rather than of the pituitary, possibly because Cushing's paper [2] had not yet appeared to emphasize the similarity of the clinical pictures produced by pituitary basophilism and tumors of the adrenal cortex. In retrospect, a number of features characteristic of pituitary basophilism are lacking in this case. There was no "rapidly acquired, peculiarly disposed and usually painful adiposity," no kyphosis, no "plethoric appearance of the skin with purplish lineae atrophicae," no vascular hypertension for six years after the clinical picture was fully established, no erythremia, and no backache or fatigability. The patient's health, as that term is usually understood, was excellent at all times, and she attended school and college during the years that she was under observation, taking part in all the usual activities.

The absence of all these characteristic symptoms is worth remarking, since some or all of them were present in the other patients described in this report. Why they should have been lacking in this patient cannot be explained, nor is speculation profitable. Another feature worth emphasizing is the definite masculinization of the voice, and its return to normal after removal of the tumor. This feature is not mentioned by Cushing as characteristic of pituitary basophilism,[2] and although it is not always present in the adrenocortical syndrome, it should be of considerable diagnostic value when it exists.

The third feature which justifies comment is the evidence afforded by the exploratory operation performed one year after masculinization had become well established. Unquestionably the tumor of the right adrenal cortex was present at that time, but it could not be palpated through the abdominal incision. It must be concluded that it was very small at that time (though the difficulty of palpating the adrenals through a median ab-

dominal incision is considerable) and therefore that even very small tumors of the cortex are capable of causing marked masculinization. The condition of the ovaries is also interesting in view of the rapid reëstablishment of normal menstruation following the second operation. At the first laparotomy they were found to be sclerosed and cystic, and were subjected to a considerable degree of surgical trauma, yet they promptly reassumed their normal function six years later when the inhibiting tumor was removed. It is, therefore, obvious that the organic pathologic changes discovered at the first operation were not the primary cause of the amenorrhea.

Case 2. A married woman, 24 years old, entered the hospital March 9, 1936, in coma.

Family History: Father, mother, and four siblings were living and well. The maternal grandmother was allergic.

Past History: No serious illnesses, no operations. As an infant, the patient was allergic to eggs, and in recent years to grass pollens, the symptoms being controlled by desensitization treatment.

Menstruation began during her fifteenth or sixteenth years, and was regular and normal until 1933, when she developed functional menorrhagia. At that time she showed a moderate secondary anemia, a basal metabolic rate of minus 21 per cent, normal blood sugar, a rather flat sugar tolerance curve. Physical examination showed slight symmetrical enlargement of the thyroid, hyperplastic breasts, and a small uterus. Three months' treatment with Antuitrin S, 200 R. U. every other day during the intermenstrual intervals, restored menstruation to normal, and it remained so until the present illness. The patient's health had been good until a week before entering the hospital, though her parents thought she seemed more tired than usual for several months before its onset.

Present Illness: February 29, 1936, while driving her car she had a brief attack of blurred vision and felt rather faint. She was, however, able to drive her car home, and after luncheon and a short rest, felt as well as usual. The next day she woke at seven, went to her sister's room for a time, and then returned to her bed for another nap. At noon her mother found her still "asleep," perspiring profusely. She was roused with considerable difficulty, and her speech was a bit incoherent. She drank a glass of orange juice, and an hour later seemed as well as ever, though she did not remember having gone to her sister's room. During the following week she felt as well as usual, but on March 9 her husband, when he went to waken her in the morning, found her in coma, and was unable to rouse her. She was seen immediately by Dr. Halsted, who found, as the only abnormal physical sign other than the coma, a palpable tumor in the left upper quadrant of the abdomen. She was taken immediately to the Faulkner Hospital, where I saw her an hour later.

Physical examination showed a well developed and nourished young woman, completely unconscious. Her pulse was not greatly accelerated, temperature normal, blood pressure normal. The pupils reacted to light, the retinae were normal, there was no choked disc, no stiffness of the neck, no abnormal reflexes. The knee-jerks and plantar reflexes were diminished but present. The heart and lungs were normal. Inspection of the abdomen showed that the left upper quadrant of the abdomen was more prominent than the right, and palpation disclosed a large mass there, extending from beneath the costal margin to about the level of the umbilicus, and from the midline outward into the flank. The mass felt resilient, and smooth. Determination of the blood sugar showed 44 mg. per 100 c.c. of blood. The plasma combining power for carbon dioxide was 51 volumes per cent. The urine showed four plus acetone.

The patient was given one liter of 10 per cent glucose solution. She regained consciousness after receiving about 50 c.c. and was well oriented and replied intelligently to questions before the infusion was completed. She stated that she had been aware for two or three weeks that the left upper quadrant was "fuller" than the right, but had thought, since she felt well, that she was merely growing fat.

The patient was seen in consultation by Dr. E. L. Young, Jr. Because of the hypoglycemia and the size of the tumor, he felt that it was probably a pancreatic cyst, and advised exploratory operation. This was done six hours later. On opening the abdomen a mass the size of a large grapefruit, bluish red in color, and highly vascular, was encountered. It was encapsulated, and across its surface ran a network of large veins. It extended backward to the posterior abdominal wall, to which it seemed fixed. There was no pedicle. A trocar was introduced and intense suction applied, but no fluid obtained. Removal by the anterior approach was obviously impossible, so a small specimen was excised with the electrocautery, and the wound closed. The pathological report on the specimen was as follows: "Carcinoma, growing with moderate speed, originating in an endocrine gland. Whether the tumor is arising from the cells of the islands of Langerhans or from the adrenal cortex cannot be positively determined from present sections. Further studies as to cell origin are being carried out." As a result of those further studies, in which several pathologists collaborated, it was then the consensus that the tumor arose from the adrenal cortex.

The patient made an uneventful though slow recovery from the operation. The fasting blood sugar, determined daily for 18 days, varied between 101 mg. and 41 mg. per 100 c.c. Readings of 60 mg. or less were obtained six times during that period. These low readings were not always accompanied by clinical symptoms of hypoglycemia. The blood counts showed nothing abnormal. Hormone assays March 23 were negative for both prolan and estrin. The patient continued to menstruate, however, for two months, but since May 27, 1936, has been amenorrheic. Postoperative roentgen-ray treatment was begun March 23, and continued until July 10, utilizing coutard dosage 258 R units. Total R units 3,200. During this treatment, she had no major hypoglycemic attacks, though she occasionally felt dizzy on awakening. Prompt relief was obtained by drinking a large glass of orange juice. Between July 10 and October 13 the attacks of hypoglycemic coma recurred frequently but irregularly; but always responded to intravenous injections of 10 per cent glucose solution. The blood pressure showed a definite upward trend, averaging during October, 150 mm. systolic and 90 mm. diastolic. A mild acne, present at the time of operation, became extremely severe, involving the entire face, the neck, chest and back, and there was marked acanthosis of the axillae. The tongue had become thickened and fissured, and the face, neck and shoulders showed marked thickening of the skin and subcutaneous tissue. Blood non-protein nitrogen and chlorides were normal, and the blood sugar normal when determined. Hormone assays were again negative for both prolan and estrin. Roentgen-rays of the skull, chest, colon (with barium enema) and kidneys (intravenous pyelogram) showed no evidence of metastases. The mass extended to the top of the fourth lumbar body, and across to the right of the spine. The colon was pushed forward and downward. It was impossible to make out the kidney outlines, but the dye reached the bladder in normal time and in normal concentration.

On October 13, a second attempt was made to remove the tumor, Dr. William E. Ladd operating, by the transabdominal route. Again it was found impossible to remove the growth. The left kidney was identified in close relation to the tumor mass, and the diagnosis of a tumor of the suprarenal cortex seemed confirmed.

Thirty-six hours after operation the patient's temperature rose suddenly and rapidly to 104.4° (rectal), the pulse rate rose from 120 to 180, and the blood pres-

sure fell rapidly to 70 mm. systolic and 50 mm. diastolic. She became comatose, reviving after intravenous glucose and adrenalin 1–1000 subcutaneously. No evidence of infection could be found. Twelve hours later she was much improved, and on the third day after operation showed a remarkable change for the better. The pulse rate had fallen to 88, temperature 101°, blood pressure normal. During the next two weeks she showed marked general improvement, especially in the skin condition. The subcutaneous thickening almost disappeared, the acne and acanthosis diminished markedly. She left the hospital November 7 in good condition.

During the next two months the patient's condition again grew slowly worse. The acne, acanthosis and subcutaneous thickening increased, though never to their former intensity. The hypertension became more marked, often reaching 190 mm. systolic and 120 mm. diastolic and occasionally going higher, and the attacks of hypoglycemic coma recurred with increasing frequency. Edema of the lower legs appeared, and shifting dullness in the abdomen could be demonstrated from time to time. During the attacks of coma the patient often became rigid, assuming a posture like that of decerebrate rigidity. At other times the hypoglycemic symptoms consisted merely of perspiration, tingling of the tongue, and moderate analgesia. During one of these mild attacks she was given, instead of glucose solution intravenously, 0.1 c.c. of adrenalin 1–1000 subcutaneously. The symptoms disappeared with dramatic promptness. Thereafter it was found that a slightly larger dose (0.3 to 0.5 c.c.) was equally efficacious in the attacks of coma, injection being followed promptly by return to consciousness, so that the patient was able to swallow orange juice within 15 or 20 minutes after the injection.

Despite the general downward progress of the disease, the patient showed surprisingly little loss of strength, and on Christmas day was able to join in practically all the family festivities. Early in January, however, she developed moderate abdominal distention, and rather frequent attacks of headache, and it was decided to use radium treatment. After consultation with Dr. Barringer and Dr. Ewing, of the Memorial Hospital, New York, she was therefore admitted to that institution on January 14, 1937, for treatment. She tolerated radium treatment well, and returned to her father's home to carry on restraint dosage of roentgen-ray. Again irradiation of the tumor was followed by cessation of the hypoglycemic attacks.

On April 9, 1937, the patient complained that during the past week her vision had been failing, especially in the right eye. Ophthalmological examination (Dr. Whitney) showed "Right eye: Disc margins clearly defined, arteries sclerotic, pinching the veins at their crossings, and veins tortuous and distended due to arterial interference. No hemorrhages seen. Left eye: Arteries sclerotic, veins normal size." Dr. Whitney's impression was that the failure of vision was due to obstruction of the venous circulation in the retinae, and also in the central vessels.

The patient's general condition showed little change. The blood pressure varied between 140 and 160 mm. systolic, and 90 and 100 mm. diastolic. The abdominal distention grew more prominent. There was variable shifting dullness, and intermittent edema of lower legs and ankles. Hypoglycemic attacks of variable intensity, always responding to adrenalin, recurred two or three times weekly. It was, therefore, decided as a last resort to treat her with the extremely powerful roentgen-rays now available at the Huntington Hospital. On admission to the hospital the patient was found to have considerable fever which subsided by lysis in three days. During her stay in the hospital this sudden rise in temperature followed by a lysis recurred twice. Roentgen-ray of the chest gave evidence of metastases in the right lung. The patient had several hypoglycemic episodes while in the hospital but after completion of the treatment they did not recur. Hormone assays of specimens obtained during hospitalization were negative for prolan and estrin, but positive for the male hormone, quantitation showing between 1.5 and 2.0 bird units present.

She grew weaker and more emaciated, developed a harassing cough and marked anorexia, so that it became almost impossible to furnish an adequate amount of carbohydrates. In spite of this deficiency, however, she did not have any more hypoglycemic attacks.

Death came apparently from general exhaustion on July 8. Unfortunately permission for autopsy could not be obtained.

Comment

The outstanding symptoms in this patient contrast sharply with those of the first. In one, symptoms were fully established before the tumor could be palpated during laparotomy; while in the other, the growth had reached such size as to cause visible tumor of the abdomen before severe symptoms appeared. This fact alone would suggest that the two tumors were different in nature.

Even more convincing, however, is the hypoglycemia encountered in association with the growth. The patient's blood sugar was normal when it was determined three years previously, and she had had no symptoms suggesting hypoglycemia until 10 days before the tumor was discovered. It is hardly likely, therefore, that the former antedated the latter. The mechanism by which an adrenal cortical tumor produces hypoglycemia is far from clear, and a careful search of the literature discloses no record of a similar association. In fact, hyperglycemia and glycosuria seem to represent the usual disturbance of carbohydrate metabolism in both the adrenocortical syndrome and pituitary basophilism (Cushing,[2] and Kepler et al.[1, 3, 4]) and hypoglycemia has been reported in human adrenal insufficiency by McLean.[5] Britten and Silvette [6] found diminution in blood sugar and liver and muscle glycogen in dogs, cats, rabbits, guinea pigs and rats after adrenalectomy, and produced hypoglycemic convulsions and death by removing the adrenals of opossums and marmots. It is not clear, however, whether it is the loss of cortex or medulla which produced these results.

Equally obscure is the mechanism by which small doses of adrenalin relieved the hypoglycemic attacks in this patient. The fact that it did, however, suggests that the low levels of blood sugar were due not to an exhaustion of glycogen reserves, but to an interference with its mobilization.

The further features of special interest are the amenorrhea and atrophy of the breasts, without positive masculinization; the absence of prolan and estrin from the urine, the apparent beneficial effect of irradiation upon the hypoglycemic attacks, and the changes in the skin.

The latter merits, perhaps, special consideration. The skin of the face, which had previously been normal, became thickened, dusky red, and literally covered by small acne papules and pustules. The same process extended downward over the neck, shoulders, chest and back, and in the axillae the hyperplasia of the epidermis was so severe as to produce small lobulated tumors. Following irradiation of the tumor temporary remission of the skin condition occurred.

It is, perhaps, not absolutely certain that the tumor in this case arises from the adrenal cortex. However, the anatomical findings at the second operation and the general agreement of opinion among the pathologists who have examined the sections obtained seem sufficient to eliminate all but the faintest chance that it arises from any other organ. The endocrine character of most of the patient's symptoms suggests a hyperfunctioning gland rather than a non-secreting malignant growth, and the presence of male hormone in the urine is characteristic.

Case 3. A white female of 30 years, single, American, school teacher. She was referred to the Diagnostic Hospital, April 20, 1934, by Dr. Eugene McCarthy of Rumford, Maine, because of blurred vision, of 18 months' duration, polyuria and nocturia for nine months, and amenorrhea for eight months. Dr. McCarthy's history also showed that she had felt unduly fatigued for several years, had "bruised easily, and had noticed an increasing growth of hair on her face for the past year." Polyuria and nocturia, but no polydipsia, had bothered her for about nine months before admission.

Family History: One brother died of "sugar diabetes" at the age of fourteen. Two brothers and her father and mother are living. The latter has some kidney trouble.

Past History: No operations and no serious illnesses other than diphtheria, mumps and tonsillitis in childhood.

Menstrual History: Catamenia began at 11 years of age and was perfectly regular until 1931 when it became irregular for two months and then ceased. At about the same time she noticed that her voice was becoming harsher, that she felt irritable and clumsy and that her hair was growing coarser. She had gained about 25 pounds in weight during the previous two years. She was seen at the Lahey Clinic at that time, and was found to be overweight, nervous and florid. Her heart was moderately enlarged, no murmurs were heard, the aortic second sound was accentuated. The blood pressure was 230 mm. systolic, 148 mm. diastolic. Abdominal examination was negative. Pelvic examination (Dr. McCarthy) was negative. There was edema of both lower extremities. Eye grounds showed no hemorrhages or exudate, some vascular changes but no arterio-venous nicking. The blood non-protein nitrogen was 32 mg. per cent, and the hemoglobin 85 per cent. Blood counts were normal; the coagulation time, 2 minutes 15 seconds. The urine showed a fixed gravity between 1.005 and 1.014. The Wassermann reaction was negative. A diagnosis of primary hypertension was made.

During the next three years the patient became increasingly fatigable, so that latterly it had been necessary for her to stay in bed very often for a day or two. The blurred vision, already mentioned, had been increasing steadily, and for three weeks before entrance had taken the form of a fixed spot before the right eye. The left eye was less affected, but reading, especially of fine print, had become difficult. The eye lids had become slightly puffy and it had become an effort to hold her eyes open. There had been some increase of the hair on the face, and her skin had been constantly discolored with "black and blue" spots. The lower legs, ankles, and feet were constantly swollen.

Physical Examination: A red faced, florid, obese young woman with no deformities. The obesity is localized in the abdomen and breasts, and there are fat deposits in the axillary regions. There is pitting edema of the legs and ankles, and a number of discolored areas on the legs. There are several bluish to reddish striae on the medial aspect of each thigh, and in the axillary borders. The cheeks show a fairly rich growth of hair.

The lips are slightly cyanotic, the skin everywhere dry and scaly.

The thyroid is not palpable. The lungs are normal. Heart: The apex impulse is felt 11 cm. from the midsternal line in the fifth interspace just to the left of the mid-clavicular line; the right border extends 3 cm. from the mid-sternal line; the upper border is at the third rib. There are no murmurs and no arrhythmia. The blood pressure is 220 mm. systolic and 160 mm. diastolic. The abdomen shows marked *panniculus adiposus,* but is otherwise not remarkable. All normal reflexes are obtained, no abnormal reflexes elicited.

As preliminary diagnoses at this stage of the examination both malignant nephrosclerosis and pituitary basophilism were suggested as possibilities.

A neurological examination by Dr. Golden showed no disturbance of sensation, astereognosis and no incoördination.

Laboratory examinations: Hemoglobin 103 per cent (Sahli), red count 5,500,000, blood clotting time normal. Sedimentation rate 21 mm. in one hour. Hinton, Wassermann and Kahn tests negative. Blood calcium 11 mg., cholesterol 375 mg., non-protein nitrogen 52 and 45 mg. per 100 c.c. of blood. Glucose tolerance test: Fasting blood sugar 112 mg.; 30 minutes after 100 gm. glucose, 246 mg.; one hour, 297 mg.; three hours, 172 mg. per 100 c.c. blood. Urine tests showed evidence of normal diluting and concentrating function; the phenolsulphonephthalein excretion was 49 per cent in two hours. Albumin varied between 0.1 per cent and 0.15 per cent on numerous examinations, and the sediment showed numerous fine granular and cellular casts, a varying number of white and red cells and on one occasion large numbers of the latter.

Pyelograms were essentially negative. Roentgenograms of the skull showed no evidence of tumor. A tuberculin test was negative. An electrocardiogram was normal except for left axis deviation. The blood pressure remained always above 200 mm. systolic and 160 mm. diastolic. The basal metabolism was minus 4 per cent on one occasion, and minus 8 per cent on another.

The laboratory findings made the diagnosis of malignant nephrosclerosis a very unlikely one. Pituitary basophilism remained a possibility. The masculinization, however, strongly suggested adrenal cortical tumor. It seemed advisable therefore to explore for adrenal tumor.

On May 11, 1934, Dr. Lahey operated, found and removed a "plum sized tumor" of the left adrenal. Following operation the patient's blood pressure fell to 120 mm. systolic and 90 mm. diastolic, and continued to fall, despite intravenous injections of saline, glucose and adrenalin. Eschatin was also administered but the patient died apparently from acute adrenal failure.

Autopsy showed removal of the left adrenal gland and extreme atrophy of the right. The latter was found with great difficulty, and weighed less than 0.5 gm. The capsule was thick, the medulla practically absent. Only a few cortical cells were vacuolated. The right ovary measured 3.5 by 1.5 by 1 cm. and contained three thin walled cysts, filled with clear fluid. The left ovary was wrinkled and shrunken and measured 2 by 1.5 by 1 cm.

Microscopic examination of the removed tumor showed adenoma. The pituitary body was grossly normal, showing no increase in size. Study of serial sections by Dr. Shields Warren and Dr. Eisenhardt showed no basophilism of the anterior lobe.

Anatomical diagnosis: Marked atherosclerosis; hypertrophy of the heart; dilatation of the stomach and intestines; cholelithiasis; atelectasis of the lower lobe of the right lung; hypertrophy and degeneration of the pineal gland; surgical removal of the left adrenal body.

Comment

The clinical picture presented by this patient is very similar to that described by Cushing [2] as typical of basophilic adenoma of the anterior pitui-

tary body. In fact, all the typical symptoms of that condition are present, with the possible exception of osteoporosis and kyphosis, which are not specifically noted in the record. In contrast to the other two patients there was even a slight erythremia found, and the history of fatigue and exhaustion is present. The one symptom which was not typical was the change in the voice, which, as has been noted, is not described by Cushing as occurring in pituitary basophilism. Yet, as in the case described by Walters, Wilder et al.[4] the anterior pituitary body was grossly normal, and serial sections studied by Dr. Warren and Dr. Eisenhardt revealed no basophilism. The discussion of the moot question of the relations between pituitary basophilism and adrenocortical tumor does not lie within the scope of this paper but it seems proper to reëmphasize voice change in the female as a possibly important differentiating symptom between the two conditions.

Finally, it seems worth while to call attention to the fact that in all three of the female patients reported, menstruation did not appear at the usual age. In the first and third, the menarche was unusually early, suggesting prematurity, while in the second patient it was definitely late in appearing. This may be pure coincidence in all three cases, but it seems worth noting in a paper which has for its purpose an addition to the records concerning a rare and little understood condition.

Case 4. J. K., a white 14 year old school boy, admitted to the Diagnostic Hospital, July 21, 1936, because of obesity.

Family History: Contained no account of obesity in any member of the family. There was no family history of malignancy. Four siblings are normally developed.

Past History: The father stated that the boy has never had any illnesses. He grew and developed normally until one year before admission.

Present Illness: During the past year the patient had gained weight very rapidly and his facial appearance had changed markedly due to the obesity and to a dusky reddening of his cheeks. On May 18, 1936, he had a sudden convulsive attack lasting from four to six hours accompanied by biting of his tongue and incontinence and followed by vomiting. Following the attack he returned to his normal activities and had no more convulsions. He complained occasionally of dizzy spells. At the time of admission he was attending school, having no scholastic difficulties and playing normally. There was no disturbance of vision, no polydipsia, no polyuria, no frequent headaches, no dyspnea nor palpitation, no digestive disturbance and no urinary disturbance. The obesity and change in appearance were the factors which led his parents to bring him to the hospital.

Physical Examination: A 14 year old boy of unusual appearance. The face is described as " full moon like " with thick fat folds below the chin and extending upward to merge with the cheeks. The latter were dark, cherry red. The trunk was markedly obese with prominent deposits of fat on the abdomen and on the back of the neck. The arms and legs, however, contrasted sharply in size with the obesity of the trunk, neck and face. The skin of the trunk and limbs was dry and slightly thickened and over the inside of the thighs showed marked marbleization. Here and there on the legs were a few small bluish spots, typical of subcutaneous hemorrhage. The mucous membranes were normal, musculature normal, and there was no evident deformity nor tenderness of bones with the exception of an area over the lower three ribs which was slightly tender to pressure. The skull was normal in shape. There was no evidence of exophthalmos. The pupils were wide, circular and reacted

promptly to light and accommodation. Ocular movements were normal. There was no evidence of disturbance of the third or fifth nerves. The eye grounds, both retinae and the optic discs appeared normal. There were a few hairs on the upper lip. The mouth was normal, teeth normally developed and in good condition. Tongue, pharynx and tonsils not remarkable. Save for the fat deposits previously noted there was no abnormality of the neck. The chest was broad. The lung borders were normal to percussion and there was no abnormal dullness. The breathing was vesicular. Breasts were of feminine configuration due to the fat. The heart was normal in size, sounds not well differentiated, no murmurs. The aortic second sound was moderately accentuated. The pulse was normal in rhythm. It showed increased tension by palpation; the blood pressure was 145 mm. of Hg systolic and 90 mm. diastolic. The abdomen showed a marked panniculus but was otherwise not remarkable; no masses or organs were palpable. There was marked masculinity of the type of hair growth and several dark red striae were noted on both sides of the abdomen. There was considerable hair growth in the lumbar region of the back. The genitalia were markedly hypoplastic. The extremities were freely movable and showed no deformities. Reflexes were all normal with the exception of the cremasterics which were exaggerated equally on the two sides. There was no disturbance of sensation.

Laboratory Examinations: The urine was normal and a test for prolan in the urine was negative. The blood showed a hemoglobin of 89 per cent; red blood cell count 5,430,000, Wassermann and Hinton tests negative. The basal metabolic rate varied in a number of observations between minus 20 per cent and minus 40 per cent. A blood sugar tolerance was performed with difficulty; the fasting blood was not obtained, but the values for one, two and three hour specimens after ingestion of 100 gm. of glucose were 240 mg., 299 mg. and 230 mg. respectively. The corresponding specimens of urine showed glycosuria in every specimen. Roentgen-ray plates of the pelvis and skull showed no pathologic changes.

A diagnosis of pituitary basophilism was made and he was given four treatments with roentgen-ray to the pituitary region, with complete relief of the headaches and slight loss of weight. There was little other change in his condition for the next four months. He then developed a small but deep ulceration of the anterior surface of the left lower leg which healed very slowly. His blood pressures during the four months had varied between 120 and 140. The boy seemed cheerful and had no complaints. Intravenous pyelograms gave normal findings. On April 10, 1937, it was noted that his condition was unchanged, but a few days later he developed a second ulcer just below the first. This increased rapidly in size and became as large as the palm of one's hand and discharged purulent material. The boy was, therefore, readmitted to the hospital where it was noted that the red color of the face was even more dusky. The abdominal striae were more pronounced and striae had appeared in both axillae and on the left upper arm. He had regained the weight lost after the first roentgen-ray treatments. The skin of the arms and legs had become very dry and thick and varied from bright red to bluish red in color. The left ankle was edematous and motions of the foot were painful. The fat deposits previously described had definitely increased.

The fasting blood sugar on two different days was 282 mg. and 245 mg. per 100 c.c. There was slight glycosuria. He was given insulin 25, 15 and 20 units with a reduction of sugar to normal. The omission of the insulin was not followed by an increase in the blood sugar and the boy seemed more alert. There was, however, considerable general weakness. Roentgen-rays, May 22, showed definite osteoporosis. The basal metabolism was minus 27 per cent. The glucose tolerance showed: Fasting 124 mg.; thirty minutes after 100 grams of glucose, 185 mg.; one hour, 249 mg.; two hours, 299 mg., and three hours 230 mg. The fasting and 30 minute specimens

of urine were sugar free. The one hour specimen showed a trace of sugar, the two hour 3 per cent and the three hour specimen 3.2 per cent. The sedimentation of the blood was 1.5 mm. in one hour (Westergren).

Roentgen-ray of the skull showed no evidence of tumor. The basal metabolic rate was always subnormal. Temperature, pulse and respiration were normal. Blood platelets 409,000, phosphatase 4.38 units.

The patient was transferred to the Massachusetts Memorial Hospital for exploration of the adrenal gland. His condition at the time was extremely poor and he failed to rally postoperatively, death occurring without further significant developments.

The chief findings at autopsy were as follows: There was a large symbiotic ulcer on the lateral aspect of the left leg. The right lung was partially collapsed and the right lower lobe contained a multilocular abscess approximately 4 cm. in diameter. It contained about 5 c.c. of thin, granular, purulent material. The liver was pale yellowish brown, lobulations poorly defined, distinctly greasy and somewhat friable. The pancreas weighed 100 gm. and showed many scattered subcapsular foci of fat necrosis varying from 3 to 10 mm. in diameter. The pancreatic duct showed no evidence of obstructive inflammation or other pathologic lesion. The adrenals together weighed 15 gm. and were distinctly enlarged although they showed no specific adenoma nodules. The right adrenal measured approximately 6 cm. by 3 cm. by 6 mm. The left adrenal was distinctly mal-formed and larger than the right. The upper portion seemed normal while the lower portion formed a well defined beaver-tail-like accessory lobe. It measured 7 cm. in length, 3 cm. in diameter and had an average depth of 6 mm. Serial sections showed a normal gross relationship between the medulla and cortex. No adenomatous or other tumor nodules could be seen. The cortical tissue was pale yellowish brown and showed less lipoid storage than is normally observed. The genitalia were infantile. The thymus was so extremely small and atrophic that it was found with great difficulty. Only the slightest remnants suggesting thymic tissue were discovered. The thyroid was normal in size, shape and position and appeared normal on section. The pituitary was distinctly shrunken, measured approximately 1 cm. in its long axis and 4 mm. in its diameter. It was distinctly more dense and fibrous than normal. At its left lateral pole the cut surface presented a distinct nodule approximately 3 mm. in diameter of a brighter yellow than the surrounding tissue and having no other specific characteristic. The vertebrae showed a marked osteoporosis so that in many places the dark reddish brown marrow could be seen through the outer cortical bone which could be easily incised with a scalpel.

Pathological Diagnosis: Adrenal hypertrophy; adenoma of the anterior pituitary lobe; chemical pancreatitis with extensive fat necrosis; thymic atrophy; testicular atrophy; fatty degeneration of the liver; cellulitis of the neck; symbiotic ulcer of left leg; toxic lymphadenitis. The histological findings are not yet available. Assay of the liver, adrenals and testicles for estrin showed more than 500 m. u. in the liver extract, but was negative in the other two tissues. No follicle stimulating or luteinizing hormone could be demonstrated.

Comment

Clinically, this patient presented the typical picture of pituitary basophilism described by Cushing,[2] and the pathological findings, though not complete, furnish confirmatory evidence. Postulating a primary basophilic adenoma, the other endocrinopathies can be explained as secondary manifestations of disturbed pituitary function, while no such logical sequence can be constructed if the adrenal hypertrophy be regarded as the primary

disturbance. In adrenal hypertrophy virilism, not infantilism, would be expected. No significance is attached to the hormone assays: they are reported as a matter of record.

Summary

Four cases, all presenting certain similar features suggesting the adrenal cortical syndrome, are presented. In two, the diagnosis was confirmed by operation or autopsy. In a third, the diagnosis seems reasonably established by operation, and in the fourth, an adenoma of the anterior pituitary lobe was found at autopsy. The histories, physical and laboratory findings together with the findings at operation or autopsy are reported.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

AUTO PASSIVE TRANSFER IN ALLERGY *

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On May 18, 1936 Samuel W., 52 years of age, presented himself for allergic studies because of an uncontrollable asthma that had been going on for five years. He had been examined elsewhere by the scratch method. The reactions secured by this method had not been satisfactory, in that after carrying out the eliminations suggested by these tests no relief was experienced.

On intradermal examination with standardized allergens [2] the patient reacted negatively to 80 out of 96. Of the 16 positive reactions only five could be considered unquestionably positive: feathers, black pepper, sheep wool, mushroom and corn.

There was no question concerning the allergic nature of this patient's asthma. That being the case there was every reason to believe that his circulating blood was laden with allergic antibody.

In the prosecution of scientific observations on clinical allergy, three prime factors must at all times be considered: antigen, antibody, tissue cell. The nearer we come to being able to control these factors the more trustworthy will be the interpretation of the results of experimentation. At least two of these factors may be satisfactorily controlled, antigen and antibody. The tissue cell is, and probably always will be, a variable and possibly an indeterminable factor.

The patient Samuel W. was endowed with the two essential somatic factors: antibody, tissue cell. Why, then, did his skin not react to specific antigen. Such instances are not uncommon. Specific sensitivity in such individuals is proved by the well known Prausnitz-Küstner phenomenon, brought about by the passive transfer of the allergic person's serum into the skin of a non-specifically allergic person, where, after a certain latent period, it locally passively sensitizes the skin, and when the third factor, specific antigen (allergen) is injected into it a characteristic intradermal allergic reaction develops. The Prausnitz-Küstner phenomenon was demonstrated by use of the patient's (Samuel W.) serum.

To return to the question, why did the patient's skin not react to the injection of the specific antigen, to which we had now proved he was sensitive? What difference could there be in his skin to that of a recipient's which had been proved to be non-specifically allergic but could be made passively so by the introduction of allergic serum from another person? May there be, in such instances, some unusual variation in the quantitative rela-

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tions of the circulating antibody? May there be something defective in the skin mechanism? Had something occurred to make the patient's skin less sensitive than it may have been at some other time?

I. *To test the first hypothesis* it was a simple matter to inject the patient's skin with his own antibody laden blood serum. If his skin cells were capable of being passively sensitized a reaction should occur when specific antigen is injected into the treated area because, to any antibody already circulating through the skin, there would be added concentrated antibody. When this experiment was carried out a typical intradermal allergic reaction occurred. I have designated this phenomenon as *auto passive transfer*[1] because the patient's own passively sensitizing blood serum is transferred into his own skin, where it sojourns for a certain time, then disappears. This is suggestive, but not positive, evidence that the failure of the skin to react, in the untreated areas, is due to insufficient antibody coming to it.

Method

The allergens (antigens) used were standardized[2] in my laboratory by Dr. John J. Engelfried to an exact nitrogen content of 5 mg. per cent, the same batch of allergen being used for comparative observations. Exactly 0.03 c.c. is injected intradermally as the test dose. This is done very carefully, infiltrating the skin slowly so as not to induce a traumatic reaction.

The Syringe and Needle: New B.D. Tuberculin Syringes and No. 26 (27 better) gauge rustless needles are used. After use they are carefully rinsed in warm distilled water. The needle is removed and the collar carefully cleaned with a cotton applicator and the syringe again thoroughly rinsed in distilled water. After this suction is applied by a Chapman pump which aspirates distilled water through the barrel. Alcohol (96 per cent) is then rinsed through syringe and needle to remove all traces of water. The plunger and barrel are separated and allowed to dry in the air. The needles are blown out with dry air and after checking the points, are put singly into small glass tubes between plugs of cotton to be sterilized. The syringe plunger and barrel (apart) are wrapped in heavy wrapping paper. The needles and the syringes are sterilized by placing them in an oven at room temperature, raising the temperature to 220° C., cooling to 100° C., again raising to 220° C. and allowing to cool. The needles are checked with a magnifying glass and specially sharpened, by the Department of Engineering, after they have been used approximately 10 times.

All this is done to destroy traces of allergen left in the syringe and needle, and to avoid the presence of moisture that would dilute the allergen. In other words the glassware and needles used in this investigation were chemically as well as bacteriologically sterile. Formerly our syringes and needles were rinsed in dichromate cleaning solution. This was hard on the needles. We have returned to this practice, plus the above details, as the rustless needles now used withstand this action fairly well.

Serum Transfer: A precise amount, 0.05 c.c., of the patient's serum is injected intradermally into as many skin sites as are desired. In our present routine of *auto passive transfer examination,* 32 transfers are made on alternating days. The sites or areas of transfer are tested for specific sensitivity, after 24 hours, by the intradermal injection of the standard amount of allergens (0.03 c.c.). In quite a percentage of passive transfers there is an immediate reaction following the injection of serum that cannot be differentiated from a positive allergen intradermal reaction. It disappears in the ordinary time. Its nature is considered in another paper.

Recording the Reactions: The reactions are measured in millimeters, with fine pointed dividers, in two opposite or perpendicular diameters. The average of the two readings is charted. The wheal and the area are both recorded on the working sheet. The area measurement of course includes the diameter of the wheal. The character of the wheal with regard to the number of pseudopods and the degree of edema is also recorded as well as the color of the area and its degree.

W = Wheal. E + and *E* = marked or slight edema.
P 1, 2, 3, or 4 = the number of pseudopods.
A = Area. The number gives the average diameter from which the area surface may be computed ($a = \pi r^2$)
R = red; R + very red; R — less red
F = faint; *F* = very faint; F = very very faint
M = Mottled.

Thus the following record; Ragweed $\begin{matrix} \text{W } 12 \text{ P}_2 \\ \text{A } 31 \text{ R} \end{matrix}$ means a wheal of 12 millimeters average diameter with two pseudopods and a red area 31 millimeters average diameter or, as in the following tables only the average diameters of the entire reaction at the time specified are recorded as 35 R +; 36 R —; 30 F. These are the 15 minutes, 30 minutes and one hour readings. Some reactions are, for the greater part, mottled, (M), particularly about the periphery. Measurements of these are made with the dividers to the edge of unquestioned color: observations are all made at exact time intervals announced by a mechanical timer. Seldom were measurements made excepting by myself, to assure no interference by the personal equation.

TABLE I

Auto Passive Transfer Examination

S. W., Age 52, Bronchial Asthma — May 18, 1936

Allergen	Intradermal Test in		Allergen	Intradermal Test in	
	Untreated Skin Area mm.	Auto Passive Transfer Area mm.		Untreated Skin Area* mm.	Auto Passive Transfer Area mm.
Sweet Potato	0	28 R	Lemon	0	0
Cotton Seed	0	27 R	Navy Bean	0	0
Cucumber	0	27	English Walnut	0	0
Spinach	0	23 F	Coffee	0	0
Pineapple	0	21 R	Pear	0	0
Cocoa	0	21 R	Beef	0	0
Grapefruit	0	17 R	Milk	0	0
Orris Root	0	16 R	Lima Bean	0	0
Vanilla	0	0	Cauliflower	0	0
Oat	0	0	Lamb	0	0
Cherry	0	0	Apple	0	0
Cocoanut	0	0	Rye	0	0
Silk	0	0			

* Control area on opposite side.

OBSERVATIONS

A few illustrative observations on *auto passive transfer* are recorded in the accompanying tables which are self explanatory.

Case 1. The first case is that of Samuel W., 52 years old, referred to in the opening paragraph. I made 17 transfers of the patient's serum into the skin of his back on June 24, 1936; 8 on July 3; and 16 on July 13, a total of forty-one. The following days the same number of standard food allergens [2] was injected intradermally into these transfer sites. These allergens were selected from a list of those to which the patient had failed to react on the regular intradermal examination. There resulted eight unquestioned positive reactions. These are arranged in table 1 in the order of the degree of reaction together with 14 of the negative reactions. Accordingly eight additional offenders were found by this method of examination; one of which, cucumber, was of undoubted clinical significance. The negatively reacting allergens serve as a good control.

Case 2. Mrs. Dora R., 38 years old, suffering with severe asthma, was given 96 intradermal tests in our Sensitization Clinic. No relief was secured from putting into effect the eliminations indicated by this examination. I had her sent to my laboratory where I made 11 auto passive transfers into the skin of her back (November 17, 1936). The following day these sites were tested by the intradermal injection of 11 allergens she had failed to react to. Eight of these were found to be positive (table 2).

TABLE II

Auto Passive Transfer Examination

Mrs. Dora R., Age 38, Asthma — November 17, 1936

Allergen	Intradermal Test in		Allergen	Intradermal Test in	
	Untreated Skin mm.	Auto Passive Transfer Site mm.		Untreated Skin mm.	Auto Passive Transfer Site mm.
Lemon	0	29 R	Silk	0	17 R
Wheat Leucosin	0	21 R	Grape	0	16 E
Wheat Glutenin	0	19 R	Beef	0	0
Rice	0	19 F	Cheese	0	0
Wheat Globulin	0	17 F	Lactalbumin	0	0
Wheat Proteose	0	17 R			

Case 3. Mr. G. V., 65 years old, who showed multiple sensitization in 1934, returned for reëxamination in February 1937. The putting into effect of eliminations suggested by his first examination had brought relief from his cutaneous symptoms. I made 96 intradermal tests and found him sensitive to nine. To test the effect of auto passive transfer I made nine transfers of his serum into the skin of his arms (February 22, 1937) and tested these sites the following day to nine food allergens, to eight of which he had given negative reactions on my last intradermal examination but to which he had given positive reactions in 1934. He gave definitely positive reactions to three of these (table 3).

Case 4. Willard O., 12 years old, was referred from the Otolaryngology Clinic for allergic studies because of allergic rhinitis. In 1936 he was given 32 intradermal tests and reacted to two allergens; wheat leucosin and pineapple. In February 1937 he reacted to the same two plus feathers. On March 1 we made 40 auto passive transfers into the skin of his back and tested these sites the following day by the intradermal injection of allergens he had failed to react to. He reacted to 12 of these as shown in table 4.

TABLE III

Auto Passive Transfer Examination

G. V., 65 years old — February 22, 1937

No.	Allergen	Intradermal Test in		
		Untreated Skin 1937	Auto Passive Transfer Site 1937	Untreated Skin 1934
1	Wheat Proteose	0	33 R	28 R
2	Sweet Potato	0	21 R	20 R
3	Feathers	0	15 R	22 R
4	Sheep Wool	0	14 F	20 F
5	Ginger	0	0	32 R
6	String Beans	0	0	28 R
7	Banana	0	0	25 F
8	Yeast	0	0	28 R
9	Ragweed	0	0	0

TABLE IV

Auto Passive Transfer Examination

Willard O., Age 12, Allergic Rhinitis — March 1, 1937

Allergen	Intradermal Test in		
	1936	1937	Auto Passive Transfer Area 1937
Lactalbumin	0	0	26 R
Evap. Milk	0	0	20 R
Apricot	0	0	15 R
Banana	0	0	16 R
Lemon	0	0	18 R
Orange	0	0	20 R
Sheep Wool	15	0	32 R
Cocoa	0	0	19 R
Potato	0	0	21 R
Lettuce	15	0	15 R
Cotton Seed	14	0	16 F
Peach	0	0	21 R
	12–2–36		3–20–37

Case 5. Mrs. Cassie M., 51 years old, a case of asthma, was referred from Dr. Sheldon's Allergy Clinic for auto passive transfer studies, May 21, 1937. This patient had been given 172 intradermal tests in August 1936 and had reacted positively to 85. She returned for reëxamination in May 1937 because of a continuance of her asthma. Tests for the pollens and some molds were given. Only slightly positive reactions to four were obtained. Oat grass +, rye grass +, poplar ± and June grass ±. Because of the faint reactions these tests were repeated with the same result. Table 5 records the comparative intradermal and ophthalmic tests and those of the auto passive transfer areas. Unfortunately rye grass and poplar allergens were not included. By reference to table 5 it will be seen that she gave definite reactions to nine allergens, including two she had reacted to, slightly, before.

TABLE V

Mrs. Cassie M., Age 51, Asthma. May 21, 1937

Allergen	Test 5–18–37 mm.	Auto Passive Transfer Exam. 5–21–37 mm.	Allergen	Intradermal Test 5–18–37	Auto Passive Transfer 5–21–37
Ragweed	0	0	Maple	0	33 R
Timothy	0	29 R	Alternaria	0	0
June Grass	±	27 R	*Aspergillus fumigatus*	0	28 R
Oat Grass	+	27 R	*Aspergillus niger*		24 R
Elm	0	36 R	*Trychophyton interdigitale*		0
Blue Grass		30 R			
Dandelion		32 R			

It was our understanding when this patient was sent to us that she had failed to react to the entire list of 172 allergens with the exception of those mentioned above; accordingly we had prepared her skin the day previous for 47 auto passive transfer tests. There were therefore 35 sites left; these we tested with food allergens. It is of interest to record the results (table 6), even though we do not have an intradermal control, because of the many unusually marked reactions obtained, and to illustrate for comparison how the skin may react under these conditions. I am also recording in this table the results of tests done ten months previously with the same allergens. The notation, however, is different: It is based on the appearance of the wheal without reference to the area. A wheal of about 5 mm. in diameter is recorded ±; 8 mm. +; 10 mm. ++; 13 mm. +++; 13 mm. or larger with pseudopods ++++. It is our custom to measure both wheal and area and to record a wheal of 8 mm. without appreciable area as negative. A wheal of 10 mm. as ±.

Case 6. Mrs. Irene R., aged 36, a case of asthma, was referred to me from the Clinic of Internal Medicine for auto passive transfer examination because she failed to react to any of the pollens. We made 39 auto passive transfers to the skin of her back and the following day injected seven pollen allergens and 32 food allergens. All the tests were negative.

Case 7. Robert S., 4 years old, a case of asthma, was tested with 96 antigens intradermally on March 1, 1937. He reacted to feathers only (19 mm.) On March 18, I made 16 auto passive transfers and tested the areas the following day with 16 food allergens. He reacted positively to two of these; orange, 15 mm., and potato 17 mm. The entire examination had been quite a trial to this rather nervous little chap and tears constrained me to proceed no further.

Comment: These observations, I believe, prove beyond question that an allergic person's skin which fails to react to specific allergen can be passively sensitized with his own serum; and they suggest that the inactive skin is made to react by bringing more specific antibody to it. This demonstration that an allergic person's inactive, or refractory, skin can be passively sensitized with his own serum and made to react to specific allergen, suggests that the skin inactivity may be due to a quantitative defect of circulating antibody, or to some inability of the skin cells to take up antibody as it circulates through it. However, it is of further interest to know whether an allergic person's skin that *does react* to the injection of specific allergen may be made to react more vigorously by this mechanical introduction of

more and concentrated specific antibody into it. The reactions assembled in table 7 seem to show that such more vigorous reactions may be thus induced; and add evidence that quantitative antibody influences may be responsible for failure of an allergic person's skin to react. There is, however, an instance where just the opposite result occurs, No. 8. More observations are necessary before this point can be considered definitely settled.

TABLE VI

Mrs. Cassie M., 51, Asthma Continued (See text)

Allergen	Intradermal Test 8-11-36 mm.	Auto Passive Transfer 5-21-37 mm.	Allergen	Intradermal Test 8-11-36 mm.	Auto Passive Transfer 5-21-37 mm.
House Dust	0	W 17 A 35 R	Wheat Leucosin	++	W 16 35 R
Beef	0	15	Wheat Proteose	+++	22 R
Cheese	0	0	Apple	0	W 17 31 R
Chicken	0	0	Apricot	++	20 F
Egg White	0	0	Banana	0	W 18 28 R
Egg Yolk	0	0	Grape	0	22 R
Lamb		0	Grapefruit	++	W 23 P2 40 R
Cow's Milk	0	22 R	Lemon	+++	40 R
Casein	0	0	Orange	+	W 30 P2 44 R
Lactalbumin	0	16 F	Peach		29 R
Kapok	++++	28 R	Pear	+++	W 21 P2 32 R
Pork	0	0	Pineapple	+	W 20 32 R
Barley	0	25 R	Fig	+++	W 21 24 R
Oat	0	W 18 23 R	Evap. Milk	0	14 F
Rice	0	24 R	Rye	0	19 R
Wheat Gliadin	0	0	NaCl Nipagen* Control		0
Wheat Glutenin	0	0			
Wheat Globulin	+	22 R			

* Preservative. 7.

This same phenomenon, described in connection with auto passive transfer, may also be induced through passive transfer. That is a positive intradermal reaction may be enhanced by the introduction of more specific antibody from another person into the skin. This is shown in table 8.

May there be something defective in the skin mechanism? My observations on the Prausnitz-Küstner phenomenon seem to demonstrate clearly that there is something in the skin mechanism itself that may be responsible for the degree of the skin reaction. It is easy to demonstrate that the skin

TABLE VII

Showing Instances of the Enhancing Effect of Auto Passive Transfer on the Skin Reaction

No.	Patient	Allergen	Intradermal Reaction in	
			Untreated Skin mm.	Treated Skin* mm.
1	S. W.	Corn	19	26 R
2		Mushroom	19	20 R
3		Feathers	31	46 R
4		Sweet Potato	13	28 R
5		Orris Root	13	16 R
6		Cocoa	13	22 R–
7		Black Pepper	25	30 R
8		Sheep Wool	31	17 R
9	Mr. G. V.	Wheat Proteose	28	33 R
10	Willard O.	Wheat Leucosin	24	30 R
11		Feathers	18	28 R
12		Sheep Wool	15	32 R

* Area of passive transfer.

TABLE VIII

Allergen	Intradermal Test on Untreated Area mm.	Intradermal Test on Passive Transfer Area mm.
Sweet Potato	13 F	43 R
Salmon	13 R	38 R
Mushroom	19 R	38 R
Feathers	25 R	51 R
Spinach	19 R	25 R
Sheep Wool	13 F	25 R

of different skin donors, or recipients, for passive transfer may vary greatly in its ability to react to allergen.[3, 4] For example, I record in table 9 two instances where the skin was negative to the intradermal test before passive transfer was done. After passive transfer, one reacts more vigorously than the other or does not react at all; yet exactly the same amount of antibody and the same latent period elapsed in each case before the testing was done. It is also shown in table 9 that reactions in auto passive transfer areas are as likely to occur as they are in passive transfer areas. Donor H's skin reacted oftener and more vigorously than did donor E's, and auto passive transfer areas reacted as frequently and as vigorously as the passive transfer areas of donor E.

Had something occurred to make the patient's skin less sensitive than it may have been at some other time? Reference to tables 3 and 4 furnishes illustrations of a skin, which was active a year or several months before, losing its ability to react and being made to react by means of auto passive transfer.

TABLE IX

Different Reaction Ability of Different Skin Donors to Allergen on Passive Transfer

Allergen	Intradermal Test on Skin Donor H	Intradermal Test on Skin Donor E mm.	Passive Transfer Test on Skin Donor H mm.	Passive Transfer Test on Skin Donor E	Auto Passive Transfer
Silk	0	0	51	0	0
Cotton Seed	0	0	31	19	27
Date	0	0	31	20	13
Salmon	0	0	38	0	28
Vanilla	0	0	25	0	0
Cherry	0	0	19	0	0

These observations seem to indicate that failure of an allergic person's skin to react may be due to one or a combination of two things—quantitative antibody influences; some change in the skin mechanism whereby specific antibody is not properly brought to it or is kept away from it.

Determination of the quantity of circulating passively sensitizing antibody: To carry this work further some method for quantitating or titrating circulating sensitizing antibody must be worked out, investigated and found to be satisfactory.

By using known amounts of specific antigen (allergen) the amount of antibody in a given serum may be determined by an absorption experiment. It has been shown in this laboratory and elsewhere [3, 4, 5, 6] that specific antigen

TABLE X

Sensitizing Antibody Titer

Robert M., 11 years. Short Ragweed

No.	Antibody + Antigen			Reaction in Passive Transfer Area mm.
	Serum c.c.	NaCl c.c.	Antigen mg. % prot.	
1	0.35	0.15	20	0
2	0.35	0.15	10	0
3	0.35	0.15	5	0
4	0.35	0.15	2.5	26 R
5	0.35	0.15	1	43 R
6	0.35	0.15	0	43 R+

1. Original antigen extract 0.666 mg. per c.c. in sterile 0.85% NaCl solution. 0.15 c.c. of this solution + 0.35 c.c. of serum = 20 mg. % of antigen.
2. 1 c.c. No. 1 + 1 c.c. of sterile 0.85% NaCl solution. 0.15 c.c. of this solution + 0.35 c.c. serum = 10 mg. % of antigen.
3. 1 c.c. of No. 2 + 1 c.c. sterile 0.85% NaCl solution. 0.15 c.c. of this solution + 0.35 c.c. serum = 5 mg. %.
4. 1 c.c. of No. 3 + 1 c.c. sterile 0.85% NaCl solution. 0.15 c.c. of this solution + 0.35 c.c. serum = 2.5 mg. %.
5. 0.8 c.c. of No. 4 + 1.2 c.c. sterile 0.85% NaCl solution. 0.15 c.c. of this solution + 0.35 c.c. serum = 1 mg. %.

destroys or renders inactive sensitizing antibody. Varying amounts of specific allergen (antigen), short ragweed for example, are mixed with a given amount of the serum to be tested. The mixtures are made isotonic with 0.85 per cent sodium chloride, incubated at 37.5° C. for one hour without preservative, and 0.05 c.c. of each dilution is transferred to a recipient's skin as previously described. In table 10 the strengths of the ragweed antigen added to the 0.35 c.c. of serum are indicated by their content respectively of 20, 10, 5, 2.5, and 1 milligram per cent protein. In this instance 5 mg. per cent (0.025 mg.) of short ragweed protein completely neutralizes all the antibody contained in 0.35 c.c. of the patient's serum. Antigen of the strength 2.5 mg. per cent does not. The actual amount necessary is therefore somewhere between these figures. Table 11 shows the same thing.

TABLE XI

Sensitizing Antibody Titer

M. M., 32 years. Short Ragweed 2-23-37

No.	Antibody + Antigen			Reaction in Passive Transfer Area mm.
	Serum c.c.	NaCl c.c.	Antigen mg. % prot.	
1	0.7	0.3	10	0
2	0.7	0.3	5	0
3	0.7	0.3	2.5	42 F
4	0.7	0.3	1	37 R
5	0.7	0.3	0	42 R

Walzer and Bowman [6] found that the admixture of equal parts of "the strongest pollen solution available (0.4 mg. N per c.c.)" with a hay fever patient's serum, completely neutralized the antibody only after several hours incubation. Coca and Grove [5] were unable to quantitate the reagin present in a given serum by the serum dilution passive transfer method. If in carrying out a comparative observation the same donor's skin can be used, and too much time has not elapsed between determinations, an idea of any change in the quantity of circulating antibody that has occurred during that time may be obtained. Change to another skin donor is not permissible because of the variability in the reactivity of different skins. Table 12 illustrates this point. Ten milligrams did not neutralize all the antibody according to J. D.'s skin; but between 3 and 5 mg. neutralized it according to D's skin and somewhere between 5 and 10 mg. according to B's skin. This again illustrates that the human tissue cell is a variable factor.

The sensitivity of the skin of an allergic person varies from time to time. Especially is this true of food allergy, depending as it does on the inclusion or omission of the specific food from the diet. Accordingly in carrying out quantitative observations by means of the Prausnitz-Küstner

TABLE XII

Sensitizing Antibody Titer

M. M., 32 years. Short Ragweed

No.	Antibody + Antigen			Reaction in Passive Transfer Area		
	Serum c.c.	NaCl c.c.	Antigen mg. % prot.	Skin Donor B mm.	Skin Donor D mm.	Skin Donor J. D. mm.
1	0.7	0.3	10	0	0	14 F
2	0.7	0.3	5	33 R	0	20 R
3	0.7	0.3	2.5	38 R	42 F	23 R
4	0.7	0.3	1	38 R	37 R	23 E
5	0.7	0.3	0	48 R	42 R	35 R

Showing that the human tissue cell is a variable factor.

passive transfer or the *auto passive transfer* method, there are many things that must be carefully taken into consideration, otherwise information based on the results may be fallacious.

SUMMARY AND CONCLUSIONS

1. Evidence is produced to show that the skin of an allergic child or adult which fails to react to the intradermal injection of allergens to which he is sensitive may be made to react by the passive transfer of his own blood serum into his own skin.

2. I have designated this phenomenon as auto passive transfer because the patient's own passively sensitizing serum is transferred into his own skin where it sojourns for a certain length of time, then disappears.

3. The method of procedure is described and a few illustrative cases presented.

4. These observations seem to show that the failure of an allergic person's skin to react to specific allergen is dependent upon one, or the combination of two factors; something at variance with the quantitative nature of the circulating antibody; something at variance with the skin mechanism whereby specific sensitizing antibody is not properly brought to it or is kept away from it.

5. In some instances, at least, reactions to specific allergen occur as frequently and as vigorously in auto passive transfer areas as in passive transfer areas. Usually, however, passive transfer areas give the larger reactions. It seems that reactions are as likely to occur in auto passive transfer as in passive transfer areas.

6. Positive intradermal reactions are very often enhanced by auto passive transfer.

7. Auto passive transfer may be used as a practical method of examination when passive transfer is indicated. It overcomes the necessity for a

control intradermal examination of the skin donor, or recipient. This shortens the examination period 50 per cent; on the other hand it inflicts more tests on the patient.

8. The *auto passive transfer* method cannot, and is not intended to, replace the Prausnitz-Küstner method. It is an interesting phenomenon and I believe it opens up a new approach to the study of the fundamental principles of skin allergy. If future observations confirm those here recorded, difficulty in securing a satisfactory skin donor for passive transfer will be avoided.

9. The difficulties of quantitative estimation of allergic antibody are considered, and a method presented.

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SOME PHYSICAL PHENOMENA ASSOCIATED WITH THE ANXIETY STATES AND THEIR RELATION TO HYPER-VENTILATION *

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During the past several years the world, in general, has been undergoing critical social, moral, and economic changes; and, in the present state of upheaval, an ever-increasing number of patients are observed who present a symptom-complex which is intimately associated with the individual's struggle for security, for independence, or for whatever state is presumed to assure the spiritual and material happiness of the individual. This symptom-complex is essentially a representation of the interaction between emotional and physiological factors. While not seen exclusively among persons suffering from psychoneuroses, this symptom-complex is frequently found in such persons; and its manifestations are designated as anxiety states. Patients presenting the well-known pattern of symptoms haunt the offices of physicians and specialists in every field of medical practice. They are often shunted from one physician to another, and the sins of commission inflicted upon them fill many black pages in our book of achievement.

Our present interest in this problem arose from the study of a group of patients who in addition to their anxious tensional states were suffering from so-called "convulsive seizures." We observed that they presented symptoms and signs of tetany associated with hyperventilation. During this investigation it became apparent that there are also a large number of patients (variously estimated as one-fourth to one-third of the patients seen in general practice) who have, as localized manifestations of the same mechanism, a variety of symptoms referable to many structures in the body; and in whom hyperventilation precipitates and maintains a state of hyperirritability approaching clinical tetany. The symptoms may be so well localized in some cases that local disease is suspected without discovery of universal functional disturbance.

In order to make clear the manner in which psychological disturbance alone can produce symptoms of tetany, the well known causes of tetany will first be reviewed briefly.

The symptom known as tetany is usually defined as a painful, tonic

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spasm of the muscles of the extremities. Many studies have been made in an effort to explain the manifestations which occur in the better known types of tetany. In general, tetany is thought to depend: (1) on the degree of mobilization of the calcium ion, probably the diffusible fraction; (2) on the presence of alkalosis; or (3) on the existence of tissue anoxemia.

In hypoparathyroidism, there is a reduction of the serum calcium, an increase in the carbon dioxide combining-power, and an increase in the serum phosphorus. When a state of hypocalcemia and alkalosis is present, the degree of tetany depends upon the threshold of the particular patient to the stimulus he receives.[1 to 4]

In gastric tetany, alkalosis results from loss of hydrochloric acid from the stomach,[5, 6] and increase in the carbon dioxide combining-power of the blood [7] because the following reaction takes place:

$$HCO_3 + OH \rightarrow H_2O + CO_3^{--} \text{ and } HPO_4 + OH \rightarrow H_2O + PO_4^{--}$$

It is suggested that in this disturbance in the chemical state of the blood, the diffusible calcium becomes fixed; and that the spasms which occur are really the result of alkalosis and hypocalcemia.[3, 5] Definite proof of this statement is lacking, however, and alkalosis alone may be the cause of the symptom.

In infants suffering from tetany, reduction of the serum calcium follows an increase in carbon dioxide combining-power. There is one major difference, however, i.e. that the serum phosphorus rarely deviates from the normal.[1, 8]

The so-called " bicarbonate tetany " can be induced in adults without the reduction of the calcium ion if a large enough quantity of sodium bicarbonate is ingested. If the H-ion concentration is reduced to 10^{-6} or less, tetany will occur. Although there is some disagreement,[9] it is stated [1] that the ingestion of any anion which will combine with calcium to produce an insoluble salt, will cause tetany. Included among these anions are carbonate, phosphate, citrate, oxalate, and fluoride. It is known that in normal individuals the production of tetany by the ingestion of phosphates can be accomplished only by the use of large amounts of the salt, whether it be acid, alkali, or neutral salt. In such circumstances,[10] the phosphates and the sodium ion concentration are increased, and the calcium and magnesium ions are decreased.

In rickets, during the healing stage, a form of phosphate-tetany occurs. In this state the interrelation of the calcium and phosphates is more labile, and the ingestion of normal amounts of phosphates is enough to depress the serum calcium and cause the spasm to take place.[1]

In discussing hyperventilation tetany, it is important to understand the physiological background which makes this symptom-complex more evident in anxious individuals than in others with more stable emotional control.

That the state of hyperventilation and its subsequent effects are not a

discovery of the present century, is well illustrated by the passage quoted below which was suggested to us by Dr. Sanford Larkey:

> Melancholoke folke are commonly giuen to sigh, because the minde being possessed with great varietie and store of foolish apparitions, doth not remember or suffer the partie to be at leisure to breathe according to the necessitie of nature, whereupon she is constrained at once to sup vp as much ayre, as otherwise would srue for two or three time; and this great draught of breath is called by name sighing, which as it were a reduplicating of the ordinary manner of breathing. In this order it falleth out with louers, and all those which are very busily occupied in some deep contemplation. Sillie fooles likewise which fall into wonder at the sight of any beautifull and goodly picture, are constrained to giue a great sigh, their will (which is the efficient cause of breathing) being altogether distracted, and wholly possessed with the sight of the image.
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> —DuLaurens, Andre:
> A Discovrse of the Preservation of the Sight; of Melancholoke diseases; of Rheumes, and of old age. . . . London. . . . 1559. Verso, o3s.

It will also be remembered that Shakespeare, in his *Seven Ages of Man*, in " As You Like It," refers to " lovers sighing like a furnace."

With these reminders that much of that which is to be discussed was described long ago, it is our purpose to re-word these phrases and apply new interpretations which will clarify the understanding of a problem that has been heretofore avoided or regarded superficially. Likewise, it is hoped that the plan of study and of treatment which is to be described will be used as an aid to the solution of such problems in the future.

A radical departure is made by those who believe that a physical syndrome can be provoked by an emotional state such as anxiety. In the past, most physicians have consciously or unconsciously, felt that such symptoms were manifestations of an overactive imagination; or, more likely, that they represented an attempt on the part of the patient to gain the center of attention of his family, friends or physician. However, there is no doubt that these patients with anxiety do suffer actual symptoms such as pain, as the result of changes in function or even in structure which have taken place because, and only because, of the preëxisting anxiety. This latter thesis will doubtless be met with considerable opposition from many internists and psychiatrists. It is our opinion that emotional conflicts which are permitted to continue for a considerable length of time predispose the individual to structural disease. It is presumed, therefore, that a chronic state of anxiety induced by such a conflict is of greater importance than is generally believed, and that its eradication, or more properly its resolution, is of utmost importance in preventing future structural, or so-called " organic," disturbances. The philosophical implications of this concept are consistent with modern knowledge of many symptom-complexes in medicine.

In offering an explanation of the interaction of anxiety states and the physical syndrome, we shall present the histories of a series of patients to

illustrate various combinations of the phenomena which have been erroneously interpreted as syndromes of organic disease that they resemble.

Symptoms, regardless of whether they are of somatic or psychic origin, are manifestations of disturbance of function. Although disorders of the psyche are known to occur without any recognizable effects on the soma, it should be made clear that no attempt will be made to divorce them. Disorders of the psyche represent disturbed functions of the total personality. Further, prolonged influence of disturbances in function in certain parts of the brain, notably the hypothalamus and basal nuclei, induces functional changes throughout the body which, if continued, may lead to local peripheral structural changes. In turn, these peripheral alterations in function and structure promote further psychical reactions which tend to aggravate the total process. Thus syndromes now well recognized are established, and the true basic nature of the malady as a primary disturbance in function is erroneously classified as being of organic or structural origin.

The concept which has been described is the outgrowth of the study of patients in whom the symptoms of grand mal, of angina pectoris, of peptic ulcer, of constriction of the sphincters of the esophagus, bladder and other hollow organs, and of Mèniére's syndrome, were found to be psychogenic and not primarily on local or structural bases. These patients were observed to respond to therapy directed toward decreasing nervous irritability by the use of medicaments and diet intended to diminish tissue alkalosis and tissue anoxemia. Later their symptoms were further alleviated by more prolonged methods of psychotherapy.

In the group of patients reported, the organic diseases suggested by their symptoms were ruled out by the usual diagnostic procedures, so that each was known to suffer from a "pseudo-disease" the symptoms of which, in all cases, were the result of the same cause—anxiety. It is believed that in the convulsive state there exists a generalized nervous phenomenon, of nervous origin, with explosive stimulation of the patient's muscular system. In the other disturbances a similar but more localized reaction occurs. It is an hypothesis that these various syndromes are the result of an increase of central (nervous) and general (humeral) irritability which, in some instances, leads to tetanoid contractions or to spasms in a specific locality that, in all probability, are initiated by tension and nervous strain subsequent to anxiety. It is really made possible by a physical and a chemical disturbance resulting in a localized tissue alkalosis, a tissue anoxemia, or a tissue hydremia.

Viewing these symptoms as manifestations of tetanoid contractions, or of peripheral nerve stimulation, or of both, diagnostic studies were undertaken which showed that this type of tetany differs from the recognized types of tetany, and is not associated with disturbances in calcium metabolism. Rather, it depends upon the other electrolytes and their relation to the acid-base balance.[2, 5, 11, 12, 13]

The Examination of the Patient

Among the tests performed, an exercise in hyperventilation [12] is included for several reasons. It is well to establish the diagnosis in this manner because repetition of the symptoms emphasizes to the patient the value of control of respiration. Likewise, he is relieved to discover that his symptoms are not those of organic disease, for it is demonstrated that he can produce them at will. Often the patient is so impressed and comes to have such faith in the physician's ability that contact or "rapport" is easily established, making psychotherapy more effective. The method is of value because studies of the alkaline shift in these patients can be made, and the efficacy of the various forms of treatment can be compared from time to time. In some instances, when the exercise is again given at a later date, it is observed that the induction-time, or period from beginning of the exercise to the appearance of the first symptoms, has increased; and that the intensity of the reaction has diminished. It is understood that normal persons will show the same symptoms if hyperventilation is continued long enough. The point of importance is the ease with which these patients are thrown into a state of tetany because they are on the threshold of attacks periodically or constantly.

The procedure is comparatively simple. Following a routinely complete history and physical (including neurological) examination, to exclude well-recognized disease, the following observations are repeated before and after performing the exercise: pulse rate, blood pressure; and reflexes, including Chvostek's and Hoffman's signs. Samples of urine are taken. The patient, then lying in a comfortable position without the inhibition of constricting clothing, is asked to breathe with the regulation of the hand of the examiner placed over the epigastrium. The lightest possible pressure is made, and the rhythm is initiated so that respirations occur at the rate of 18 to 20 per minute. The time-interval from the beginning of the test to the onset of symptoms is noted. Effort is made to induce a state of carpopedal spasm,[12] or a repetition of the symptoms of the chief complaint. If no reaction is obtained within 30 minutes, the procedure is discontinued. One should judge whether or not the patient is at ease. Some patients become slightly excited and do not breathe regularly, and the slight pause they unconsciously insert into the cycle is enough to maintain the normal acid-base balance. After the results are obtained, the patients are given carbon dioxide and oxygen inhalations (30 per cent CO_2 to 70 per cent O) to relieve the spasms or other symptoms. (Having the patient hold his breath or re-breathe into a paper bag may likewise clear off the symptoms promptly.) While this improvement is being accomplished, with the patient breathing at the same rate as before, the procedure is explained to the patient in non-technical language. Simple comparisons are made to demonstrate to him the mechanism involved; and conclusions are drawn illustrating to him his rôle in the production of his own symptoms, and to show how easily and

simply he may regain his former feeling of well-being. Should the patient not coöperate well, calcium chloride, 5 c.c. of a 10 per cent solution, may be given intravenously; and the reactions may be explained later when the patient is more quiet.

Protocols of Examples of Several Types of the Anxiety States

Below are the histories of a group of patients, illustrating the various types of responses which follow the common prodromal symptoms. Typically, all of these patients give a story of an encounter with some difficulty which causes emotional stress and anxiety. There is palpitation and tachycardia, hyperpnea, and a feeling of great weakness and fatigue. Within a variable period, there follow paresthesias of the hands and feet, and isolated muscular contractions which are associated with pain or tension similar to the symptoms mentioned in the patient's chief complaint. The characteristic local responses of which the patient complains are repeated quite regularly in successive attacks.

Group I

Tetany

Case 1. D. E., female, aged 24, separated (Case 6, Chart 1).

Chief complaint: Spasms of the hands and feet, duration one month.

Present illness: Two years before entry the patient had experienced numbness in both hands, which had responded to intravenous iron medication. Six months prior to entry, while sitting in a theater, she found that she was unable to swallow because of stiffness of her throat muscles. Two months before entry she had severe headaches for which she again received intravenous iron therapy. At this time she started proceedings for a divorce. Shortly after, she experienced gaseous distention and diarrhea. She became worse following alkalinization. One month prior to entry, while in her lawyer's office she noticed numbness of her hands and feet and a "puckering" sensation about her mouth. Later she had stiffness of the muscles of her hands and feet. Subsequent attacks progressed to the typical carpopedal spasm of tetany. Paresthesia of the skin of the chest-wall was noted. The patient stated that carbonated water alleviated these attacks.

Past history contributed nothing.

Family history: Her father, aged 49, and mother, aged 48, were living and well. They had been separated for years.

Marital history: The patient had been married for four years. Her husband drank considerably. There had been recent separation, and divorce had been obtained.

Physical examination: All findings were negative or within normal limits. The only pertinent observation was that the patient talked very hurriedly and took many deep breaths.

Neurologically, perception by senses was normal throughout. Muscles were equal and active in all movements. Reflexes were not hyperactive and were equal.

Laboratory tests: Urine, stool and blood were within normal limits. Gastric analysis; absence of free HCl, but normal response to alcohol meal. Blood calcium; total 8.67 mg. per cent; diffusible 4.62 mg. per cent.

Hyperventilation exercise: Trousseau's and Chvostek's signs, though negative at the start, became positive within 40 seconds. At four minutes, numbness of the

mouth and fingers with coolness of the knees occurred; at six minutes, stiffness of the mouth and adduction of the right thumb; at eight minutes, typical carpopedal spasm. Four minutes after inhalations of a mixture of O_2 (95 per cent) and CO_2 (5 per cent) were started, the patient returned to a normal state.

Psychiatric consultation revealed that the patient had considered herself an invalid after a doctor had told her that "she was not one of the 90 per cent who would get well."

Progress: After the demonstration, the patient became convinced that the convulsions were due to her method of breathing. She was placed on a diet and given medication to increase calcium intake and to decrease the pH of the blood. Up to the present, four months after discharge, she has had no recurrence of attacks.

Case 2. A. H., female, aged 58, widow (Case 2, Chart 1).

Chief complaint: Spasms of the hands and feet, duration one year.

Present illness: The patient first noticed symptoms while riding in an open car. She first felt irritated, then weak; then experienced numbness of her hands and later stiffness of the hands and feet. One year following her husband's death she collapsed in a theater. She had another seizure typical of tetany when she witnessed an automobile accident.

Past history: Non-contributory except for information included under "Marital history."

Marital history: The patient had been married at the age of 24; she had one son. As a family, they were affectionate. She and her husband were always told that they appeared very young, and she dressed accordingly. When her husband died, she realized that she was not young; and she felt, because her son was to be married, that she had little to live for.

Physical examination: Findings were within normal limits. The overuse of cosmetics was obvious. Neurological examination showed hyperactive reflexes.

Laboratory tests: Results were well within physiological limits. For report of blood-chemistry see chart 1.

Hyperventilation exercise: At 16 minutes, band-like headache; at 18 minutes, patient felt weak; at 21 minutes, she had numbness of both hands; at 22 minutes, paresthesias were noticed; at 23 minutes, carpopedal spasm of both hands occurred. Chvostek's sign although negative before, became positive 3° bilaterally; the reflexes were markedly increased.

Course: Within one month after entry, her depression regarding the death of her husband and fear for the future had disappeared. Two attacks started, but she was able to prevent spasms by holding her breath and "counting to ten." Within two months self-control had been completely regained.

Case 3. M. R., female, aged 21, single.

Chief complaint: Convulsive seizures, duration six weeks.

Present illness: The patient had periods of fatigability followed by irritability and then flushing of the face, chest and arms, terminating in headache. Seven weeks prior to entry she noticed that she had swollen eyelids and a distended abdomen. She sought medical advice and a vaginal examination was made in the course of the investigation; abdominal cramps followed this. She then noticed that her jaws became stiff, and that her hands and arms ached. The next day her hands and feet became stiff, and every day after that she had four or five such attacks, which were carpopedal spasms. Systems: The patient had had insomnia; distention of the stomach; and nocturia once or twice nightly.

Physical examination: Findings were normal, including neurological examination, save for slightly dilated pupils and hyperactive reflexes.

Laboratory tests and roentgen-ray examination: Urine, blood and spinal fluid were normal. Wassermann and Kolmer reactions were negative. Encephalogram showed no abnormality. Glucose tolerance test was within limits of normal. Gastric analysis showed the following figures for free acid: Fasting 90°; 1st specimen, 0°; 2nd, 20°; 3rd, 40°.

Hyperventilation exercise reproduced her symptoms, and these were relieved by inhalations of CO_2.

Follow-up report: The patient returned after six weeks, at this time feeling well. She was examined by an obstetrician who made a diagnosis of pregnancy, whereupon she had another attack of tetany from which she recovered. When last seen she had been well for three months on an acid-ash diet and ammonium chloride.

Comment: This patient's condition was a rather typical example of hyperventilation tetany without other symptoms. Her neurosis was initiated by the collapse of a romance because it conflicted with her almost mid-Victorian ideals of conduct. The original cause has not been removed, but she is symptom-free because she knows how her symptoms are produced and can prevent them.

Case 4. C. C., female, aged 42, single (Case 3, Chart 1).

Chief complaint: Muscular cramps of the hands and feet.

Present illness: The patient had a feeling of air-hunger accompanied by dyspnea, numbness of the hands and feet, and then spasms of the hands and feet similar to carpopedal spasms.

Physical examination: Findings were normal throughout, including activity of reflexes.

Hyperventilation exercise reproduced her attacks, which were controlled by inhalations of carbon dioxide. Ammonium chloride was of little value; the best results were obtained by conscious control of respiratory frequency.

Remarks: This case is introduced to show that some patients respond to one type of therapy when the usual methods fail. This woman's neurosis was controlled without the aid of measures usually classified as psychotherapeutic.

Case 5. N. A., female, aged 17, single.

Chief complaint: Generalized eczema; malnutrition; and spasms of the hands and feet.

Past history: This girl had a definite family history of allergy; and over a period of years she had been suffering from intermittent attacks of an allergic dermatitis which had responded indifferently to local treatment. She was subject to attacks of general malaise, cough, dyspnea, and pain in the chest accompanied by a sensation of air-hunger. She hyperventilated and developed carpopedal spasms with paresthesias of the hands and feet.

Physical examination: Poorly developed and poorly nourished girl with crusted lesions over the neck and face. Her condition was normal otherwise save for hyperactive reflexes.

Laboratory tests: The urine was acid. The blood was normal. Serum calcium: 10.7 mg. per cent. Blood iodine: No. 60 (normal No. 110). Basal metabolic rate 6 per cent minus. She was found to be somewhat sensitive to cereals and to carrots.

Hyperventilation exercise: Tetany could be produced volitionally and controlled by holding her breath. The patient was able to control, also, all other spasms by this method.

Comment: This patient is presented to illustrate two types of response of the autonomic nervous system: the allergic manifestation, which is said to be of the parasympatheticotonic group; and the tetany, which is thought to be a sympatheticotonic response. Her neurosis was thought to be due to restrictions of her social life

because of her long standing skin disease. The cause of the neurosis was not removed completely; but abatement of the skin lesions through treatment helped considerably.

Group II

Evidence of Generalized Muscular Irritability without Actual Tetany

Case 6. B. K., female, aged 40, married.

Chief complaint: Headache over the right orbit.

Present illness: At times this headache was likewise felt over the entire right side of the head. She had nervousness and irritability which were made worse by the taking of citrate of magnesia for chronic constipation. These symptoms were aggravated by visits to her mother-in-law.

Physical examination: Negative throughout save for hyperactive reflexes and 1° Chvostek's sign.

Laboratory tests: The urine was alkaline. The blood was normal. Gastric analysis showed absence of free acid in the fasting specimen and following an alcohol test-meal, and 46° after administration of histamine. The basal metabolic rate was 15.4 per cent minus.

Progress: The patient's symptoms were controlled by medical therapy but at no time were there more alarming symptoms than those mentioned in the "present illness." It was felt that if medical therapy had not been instituted she would have progressed to a convulsive state.

Case 7. L. S., female, aged 53, married.

Chief complaint: Nervousness and irritability for seven years.

Present illness: After menopause and its symptoms had disappeared, this woman had a severe injury to her hand which occurred on the day of her mother's funeral. Since that time she had suffered a feeling of impotence and weakness, with trembling and profuse sweating.

Physical examination: Restless patient, with hyperactive reflexes. Blood pressure: 176 systolic and 110 diastolic. Normal intercourse had been impossible because of sclerosed hymen.

Laboratory tests: Urine and blood were normal. Gastric analyses showed free acid to be absent after administration of alcohol and histamine.

Hyperventilation exercise caused merely irritability and trembling; there were no symptoms of spasm

Progress: This woman improved following the use of dilute hydrochloric acid with her meals, and sodium acid phosphate 0.3 gm., three times daily.

Group III

Severe Convulsive State Simulating Grand Mal

Case 8. H. B., male, aged 27, married (Case 11, Chart 1).

Chief complaint: Convulsions during past eight years.

Present illness: While painting his car, the patient fell unconscious and remained so for nearly 45 minutes. On recovery he felt weak and stiff. There is no history of incontinence of urine or stool. The patient had had no injuries. During any excitement or following any argument, these attacks recurred. As described by his wife, during attacks the patient became pale and fell to the ground with generalized tonic and clonic convulsions. These episodes had no apparent resemblance to carpopedal spasm. The patient had similar attacks at night. In recent years he has injured his mouth in these spasms.

Past history: The patient was a coffin-maker. He had been married for the second time; his wife was frigid.

Physical examination: Thin, asthenic male who appeared to be younger than stated age. The findings were normal save for Chvostek's sign of 1° on the right and 2° on the left.

Hyperventilation exercise: At 5 minutes, numbness of hands and feet; at 9 minutes, adduction of the right thumb; at 11 minutes, carpopedal spasm; at 13 minutes, generalized tonic and clonic convulsions with spasm of the masseter muscles. There was no incontinence.

Laboratory tests: Negative throughout save as shown in chart 1.

Progress: The convulsions were not controlled until he was placed on an acid-ash regime, with calcium and parathormone. It was noted on his return visits that the time-interval between attacks became greater and the degree of response to the hyperventilation was much less.

Case 9. M. L., female, aged 29, married.

Chief complaint: Convulsions, duration 9 months.

Present illness: Generalized muscular irritability preceded the onset of tonic spasm with opisthotonus. There followed clenching of the fists with kicking of the feet. Next, precordial pain occurred, with radiation down the right arm. The patient never injured herself; and had no incontinence. The seizures occurred every 4 to 6 weeks, and usually followed altercations with the family.

Physical examination: Reflexes hyperactive; otherwise negative.

Laboratory tests: Examinations of urine, blood, stool, and spinal fluid, and gastric analysis were negative. Basal metabolic rate 6.7 per cent minus. Roentgen-ray examination showed no evidence of an intracranial lesion.

Hyperventilation exercise produced trembling, dizziness and a feeling of faintness, and reproduced the tonic state described above which was not a form of tetany. Her husband said that this response was the same as that which occurred in her attacks. Before hyperventilation, examination of urine by Folin titration method showed 150° (c.c. 0.1 normal NaOH), and after hyperventilation, 36°, which indicates a definite shift to the alkaline side.

Comment: This patient, although in a general convulsive state, has a history which suggests hysteria. She improved after developing self-control of this mechanism, and has had many less seizures.

Group IV

Localized Spasms of Muscles, with Symptoms Simulating Those of Cardiovascular Disease

Case 10. F. S., female, aged 27, married (Case 10, Chart 1).

Chief complaint: Precordial pain for 1½ years.

Present illness: This patient suffered weakness, easy fatigability and twitching of the muscles of the body for a short time prior to the onset of the chief complaint. She then noticed severe pain over the precordium, which radiated down the left arm. There was no dyspnea until later, but she had nausea and eructation. Just before entry a right occipital headache developed with some photophobia.

Physical examination: Thin, nervous woman who cried easily. She appeared to be of the stated age. Her heart was not enlarged; sinus arrhythmia was present; there were no murmurs. Blood pressure systolic 110; diastolic 80. Reflexes were hyperactive. Chvostek's sign was 1° on both sides.

Laboratory tests: Blood and urine were normal. Tuberculin test was negative. Phenolsulphonephthalein test: total 60 per cent. Mosenthal test showed no fixation and good concentration. Electrocardiogram showed evidence of sinus arrhythmia and T-waves diphasic in Leads I and II, inverted in Lead III.

Hyperventilation test: At three minutes, tachycardia; at eight minutes, hysterical crying; at eleven minutes, stiff lips and numbness of hands; at 15 minutes, adduction of the left thumb; at 17 minutes, carpopedal spasm, and pain recurring over the heart. See chart 1 for reports of blood and urine chemistry.

Comment: This patient's neurosis was based on fear. Her brother-in-law had killed his wife and his wife's family. The patient feared that her husband would do the same. The combination of psychic purgation and the use of ammonium chloride were sufficient to control symptoms of the complaint for three months.

Case 11. J. A., female, aged 32, married (Case 4, Chart 1).

Chief complaint: Precordial pain for two years.

Present illness: The patient had onset of acute pain over the precordium, felt particularly on effort. There was radiation of the pain to the left scapula. Attacks of diarrhea followed these bouts of pain, which occurred also when the patient was present at public gatherings and after she drank alcoholic beverages. Before entry she noticed stiffness of the hands and feet without actual spasms of the muscles.

Physical examination: Negative throughout except for the hyperactive reflexes and a positive Chvostek's sign bilaterally.

Laboratory tests: See chart 1 for all positive findings. Stools were negative for organisms and parasites which cause diarrhea.

Hyperventilation exercise: At the end of 21 minutes there was a reproduction of the symptoms of pain in the region of the scapula and precordium; also of the numbness and stiffness of which she had complained. The Chvostek's sign was 3° bilaterally.

Comment: This patient's neurosis was founded in dislike of her father-in-law. She was led to understand the source of her symptoms, and to be able to control them through regulation of her respiratory rate. She was placed on the acid-ash regime. Her symptoms disappeared and did not recur. The cause of this patient's neurosis could not be removed.

Case 12. D. G., female, aged 35, married (Case 13, Chart 1).

Chief complaint: Rapid heart rate and precordial pain.

Present illness: This patient noticed that after emotional upsets and altercations, she was unable to inspire enough air for her need. Later she had onset of severe and persistent tachycardia without palpitation. A distressing tension was felt about her heart without actual pain.

Physical examination: Reflexes were hyperactive; Chvostek's and Trousseau's signs were negative.

Laboratory tests: For the positive findings, see chart 1.

Hyperventilation exercise: At three minutes, dryness of the month; at five minutes, stiffness of the hands and feet; at 10 minutes, diaphragmatic constriction with momentary pain under the left breast simulating the chief complaint. Hoffmann's, Chvostek's and Trousseau's signs remained negative.

Comment: As the cause of this patient's neurosis was never discovered, it is doubtful that permanent cure was effected. However, at her last visit, she had been symptom free for one month.

Case 13. M. M., female, aged 36, divorced (Case 15, Chart 1).

Chief complaint: Palpitation and precordial pain, duration one year.

Present illness: Following the nursing of her mother through a fatal attack of angina pectoris, this woman had insomnia for three weeks and lost 16 lbs. in weight. She suffered an attack of palpitation which was mitigated by quinidine. She developed pain over the precordium pressure-like in character, which radiated to her left elbow.

Physical examination: The patient had the physical signs of rheumatic heart disease with mitral stenosis and insufficiency.

Laboratory tests: Results are recorded in chart 1. Electrocardiogram showed evidence of delayed A–V conduction, slurred Q–R–S complexes and upright T-wave in Lead IV.

Hyperventilation exercise produced rapid heart-rate in addition to the symptoms of the chief complaint.

Comment: This case shows that a neurosis may overlie organic disease, making it difficult to evaluate the symptoms of the organic lesion. However, the patient clinically did not have the type of heart lesion that would be expected to give rise to the symptoms of which she complained. In such instances the patient, even though symptom-free, should be kept under observation in order to follow the progress of the organic disease.

Case 14. M. M., female, aged 23, married (Case 16, Chart 1).

Chief complaint: Rapid pulse and pain over heart.

Present illness: Following the death of her father, this woman became irritable; but it was not until after the birth of her child that she noticed rapid heart rate and pain over her heart experienced on effort. She had dyspnea on exertion. The pain did not radiate to her arms or neck. She did not have the symptoms of irritability that had bothered her at first.

Physical examination: Negative save that the patient was very nervous and was observed to sigh frequently during the course of the examination.

Laboratory tests: See chart 1 for changes after hyperventilation. Free acid was low in the gastric content (between 4° and 8° even after injection of histamine).

Progress: The patient's recovery was more protracted than that of most patients; administration three times a day of 8 gm. of ammonium chloride after meals and hydrochloric acid 1 c.c. with each meal were required. After two months on this regime she had no tachycardia and only occasional episodes of hyperventilation.

Case 15. T. W., female, aged 35, widowed.

Chief complaint: Palpitation.

Present illness: Following the injection of novocaine for some dental work the patient had a hysterical attack of crying which ended in a tetanoid spasm accompanied by paresthesias. Her father died from coronary occlusion, and throughout his illness the patient nursed him. Shortly thereafter, she became subject to pain over the precordium which did not radiate to the arms but which was associated with the symptoms of fatigue, paresthesias and stiffness of the extremities. These attacks occurred when she was emotionally distressed, particularly about finances and about her health.

Physical examination: The patient had a splenomegaly, the cause of which was not discovered; she had hyperactive reflexes and a 1° Chvostek's sign.

Laboratory tests: Essentially normal results were obtained throughout.

Hyperventilation exercise produced the typical carpopedal spasm after 38 breaths were taken. The symptoms of the chief complaint were reproduced. These were relieved when the patient held her breath. Exercise for determination of cardiac efficiency produced the same symptoms.

Comment: This patient is another illustration of the hyperirritable individual who assumes the symptoms of the illness of a person with whom he has had intimate contact. It is felt that these symptoms are not imagined, but are really manifestations of local spasms of the intercostal muscles and possibly of the diaphragm.

Group V

Vascular Disturbances: Pseudo-Raynaud's Disease

Case 16. M. T., female, aged 54, widowed.

Chief complaint: Numbness of the hands.

Present illness: This woman had had considerable difficulty with her husband and had been separated from him before he died. She suffered from irritability, faintness, easy fatigability, and paresthesias of the hands. Later she noticed that when she was excited, the fingers of both hands became blanched in corresponding areas. These changes occurred likewise on exposure to the cold. Still later she began to have a feeling of air-hunger and a choking sensation in the throat.

Past history: In 1924 this patient had a sub-total thyroidectomy for Graves' disease. At that time she had positive eye-signs, an enlarged thyroid gland with a bruit, and basal metabolic rates of 59.5 and 22.9 per cent respectively on two occasions. At operation she was found to have a thyroiditis. In September 1927, her basal metabolic rate was 7.5 per cent minus.

Physical examination: The patient had nothing about the hands which suggested capillary instability. Her reflexes were active.

Laboratory tests: Negative save that gastric analyses showed no free acid in the fasting contents and only 8° after histamine was administered.

Hyperventilation exercise reproduced the blanching of the fingers bilaterally in corresponding positions, the areas increasing with the degree of hyperventilation. The same reaction was produced by immersing the hands in cold water.

Comment: This patient apparently illustrates the spasm of vessels to a marked degree. The reaction did not cause a true tetany but only a stiffness of the hands. She was placed on NaCl, 1 gm. three times a day and HCl given by mouth, and her vascular disturbances have decreased considerably although they have not as yet entirely disappeared. We have observed several patients in the clinic who presented local blanching and cyanosis of the fingers (Raynaud's syndrome) whose local symptoms cleared promptly upon holding the breath or breathing CO_2.

Group VI

Disturbances Simulating Diseases of the Chest, Mainly of the Asthmatic Type

Case 17. C. D., female, aged 55, married (Case 14, Chart 1).

Chief complaint: This woman had a sense of choking and suffocation at the onset of her menstrual periods. No other symptoms occurred until she was 45 years of age when she suffered pain down her arm and paroxysmal dyspnea. She was observed at this time and has been examined frequently since for angina and more recently for coronary disease. No definite evidence has been found of the existence of coronary disease. These symptoms became worse when she had to care for her paralyzed husband whom she did not love and who was 20 years older than herself. She suffered extreme weakness and easy fatigability and had a sensation of clutching compression of the throat which would cause her to gasp for air. She had pain down the left arm during severe seizures.

Physical examination showed hyperactive reflexes. The cardiac findings were within normal limits.

Laboratory tests: See chart 1 for reports of chemical tests on the urine and blood. Basal metabolic rate 32.6 per cent minus. Electrocardiogram showed left axis deviation and flat T-waves.

Hyperventilation exercise: At 60 seconds there was fixation of the diaphragm; at 80 seconds, cyanosis of the nose and fingers; at 90 seconds, marked spasm of the bronchial and tracheal muscles, with a generalized convulsive spasm of the bronchial

and tracheal muscles, with a generalized convulsive seizure in an effort to regain breath. During the process she developed a 2° Chvostek's sign. Trousseau's sign remained negative.

Comment: As well as being an excellent example of simulated asthma, this patient was remarkable because of the exact regularity of the cycle of her reactions. One could predict within the second what type of response would occur. She recovered rapidly following inhalations of CO_2, and has remained without major symptoms on an acid-ash regime.

Case 18. M. H., female, aged 45, separated.

Present illness: The patient had symptoms of fatigue and weakness, paresthesias, and stiffness of the hands and feet. She came to the Clinic with the complaint of a sensation of constriction in the neck; and a lump was noticed there. She was thought to have thyrotoxicosis. Constriction of her throat caused considerable dyspnea and attacks similar to those of asthma.

Physical examination: A small nodule was found at the left lower pole of the thyroid. There were no signs of toxicity, however.

Laboratory tests: Urine and blood were normal. Basal metabolic rate 6.4 per cent minus. Gastric analysis: 17° free acid in the fasting specimen, with normal response to instillation of alcohol.

Hyperventilation exercise produced paresthesias of the hands, increase of reflexes and a sensation of constriction of the throat.

Progress: No observations were recorded as to the results of therapy. This patient was less troubled by her symptoms than was the patient described above (Case 17).

Case 19. J. B., male, aged 46, married.

Chief complaint: Dyspnea.

Present illness: This man had epigastric pain simulating that of ulcer of the duodenum, and he had been treated with alkalies for years. He became a morphine addict, and he contracted syphilis. Because of fear of his disease he became irritable and had dyspnea on exertion. Later he began to have a tense feeling in his throat. He had constipation because of his morphine addiction.

Physical examination: Findings were normal in every respect.

Laboratory tests: Urine was alkaline. Blood was normal. Spinal fluid examination was negative. Roentgen-ray examination: Gastrointestinal series was negative. Gastric analysis: Normal amount of acid.

Ventilation was observed and the symptoms were seen to increase in the process. A formal experiment was not performed.

Progress: Response to treatment was not rapid here because of the morphinism. Some improvement was noted after reassurance was given, as well as after the use of the acid-ash regime.

Group VII

Simulation of Thyrotoxicosis

Case 20. L. J., male, aged 25, single.

Chief complaint: Numbness of the hands.

Present illness: For two years the patient had experienced nervousness, tachycardia and palpitation. He was easily fatigued. His basal metabolic rate was 14 per cent plus, and a subtotal thyroidectomy was performed. Following this operation, symptoms of tachycardia and palpitation decreased but the paresthesias of the hands persisted.

Physical examination: Asthenic male with hyperactive reflexes.

Laboratory tests: Blood and urine were normal. Gastric analysis showed an absence of free acid even after injection of histamine. Basal metabolic rate, 34 per cent minus.

Hyperventilation exercise reproduced the symptoms of the hyperthyroidism and the paresthesias of the hands.

Progress: The patient was placed on a high salt intake and improved slightly. He was then given HCl by mouth.

Comment: This man and others of this group are examples of a type of patient appearing in the thyroid clinic who is not thyrotoxic but who has a neurosis giving similar symptoms.

Case 21. M. M., female, aged 37, married.

Chief complaint: Nervousness following an operation.

Present illness: The patient had been nervous for the past five years. She had tremor, intolerance to heat, increased appetite, and a loss of 10 lbs. in weight. She noticed a sudden enlargement of the left side of her neck, and visited a doctor. At this time she had dyspnea on exertion and nocturia. On examination the left lobe of the thyroid was found to be enlarged. The basal metabolic rate was 44 per cent plus. An adenoma of the thyroid with hemorrhage was diagnosed, and was found when thyroidectomy was performed. Six months later the patient returned to the clinic. Save for the absence of the swelling, she had at this time the same symptoms that she had had at previous entry.

Physical examination was negative.

Laboratory tests: Gastric analysis showed absence of free acid, but a normal response to alcohol test-meal.

Hyperventilation exercise reproduced all of her symptoms.

Progress: This patient improved greatly following the use of ammonium chloride and the institution of an acid-ash diet. Her symptoms are now controlled. The neurosis was not cured because it was caused by the marital status which has remained unchanged.

Case 22. L. F., female, aged 25, married.

Chief complaint: Nervousness and fullness in the neck.

Present illness: For six years this woman had noticed increasing irritability. There were tremor and nervousness, palpitation, tachycardia and intolerance to heat. On several occasions she had hysterical upsets.

Physical examination showed an adenoma of the thyroid. The basal metabolic rate was 18.6 per cent plus. Radiation with roentgen-ray was begun, and two months later the basal metabolic rate was 8.5 per cent minus. After four years she returned with the same symptoms. It was learned that, while she was living at her uncle's home, she had a clandestine romance with him which she was unwilling to stop, and which was in constant danger of exposure.

Laboratory findings were within normal limits.

Hyperventilation exercise reproduced all of the symptoms of the present illness.

Progress: At the present time she has shown improvement under medical therapy. Psychotherapy is being directed toward helping her to establish some sort of decision as to her relationships in the future. This patient was not operated on, as were the former patients; but it is believed that her adenoma is not toxic.

Case 23. E. H., female, aged 29, married.

Chief complaint: Nervousness for four years.

Present illness: Four years ago the patient began to notice a feeling of weakness

and increasing nervousness. She had loss of emotional control. During the next year an enlargement appeared in her neck and she noticed that her heart rate was rapid and that she had increased perspiration. Treatment with Lugol's solution caused improvement. One year before entry she returned to the clinic with palpitation and dizziness. She had lost four lbs. She had dyspnea and a sense of tension in the chest on inspiration.

Physical examination: There was slight enlargement of the right lobe of the thyroid. She seemed to be more nervous than the signs of thyrotoxicosis would warrant.

Laboratory findings were entirely normal.

Hyperventilation exercise reproduced the symptoms of palpitation and dizziness and the sensation of constriction in the chest.

Comment: The results of treatment cannot well be evaluated here because of an involved social history which has not been completely obtained. The exercise aided in establishing a contact with the patient which has been very helpful in psychotherapy.

Group VIII

Gastrointestinal Disturbances

Case 24. F. H., male, aged 35, single (Case 12, Chart 1).

Chief complaint: Epigastric pain.

Present illness: This man suffered severe weakness and nervousness and muscular twitchings. He developed midepigastric pain followed by gas pains, at first occurring after meals and later having no relation at all to meals.

Physical examination: Hyperactive reflexes and 1° Chvostek's sign were found.

Laboratory tests: See chart 1 for urine and blood findings.

Hyperventilation exercise produced the muscular twitchings in six minutes and generalized muscular contractions in nine minutes.

Progress: This man's symptoms were relieved by the acid-ash regime which of course is directly opposed to the usual method of treating peptic ulcer.

Case 25. W. R., male, aged 27, single (Case 17, Chart 1).

Chief complaint: Epigastric pain relieved by food.

Present illness: The patient's pain occurred in the epigastrium before meals and was relieved by food and soda. The pain radiated to the back under the left scapula. There was no nausea and no vomiting or melena. This man also suffered a sense of suffocation and tightening of the facial muscles when he talked or laughed too much.

Physical examination: Perspiring, nervous and asthenic male appearing to be of the stated age. Reflexes hyperactive and equal.

Laboratory tests: All findings were normal save that the gastric analysis showed no free acid and only 22° after injection of histamine. Gall-bladder visualization was negative. See chart 1 for reports of the blood and urine chemistry.

Hyperventilation exercise reproduced the epigastric pain and produced carpopedal spasm. Chvostek's sign 2° was observed bilaterally.

Comment: This patient had obvious signs of tetany but associated with it were the symptoms of the complaint. He had suffered from atrophic arthritis and it was felt that his discouragement over the progress of this disease was the basis of his neurosis.

Case 26. R. S., female, aged 45, married.

Chief complaint: Eructations of gas from the stomach.

Present illness: Since the age of 18 the patient has had gas pains for which she had taken soda and at intervals she has had periods of dizziness. Ten years before

entry, following an operation for tonsillectomy she had a recurrence of the spells of dizziness. For two years she is said to have had tarry stools following these attacks.

Physical examination: Entirely negative.

Laboratory tests: Urine, blood and stool were normal. Gastric analysis: No free acid after instillation of alcohol, but 62° after injection of histamine. Roentgen-ray examination: Gastrointestinal series and barium enema were negative.

Hyperventilation exercise produced diaphragmatic spasm, belching and hiccoughing. This patient demonstrated fixation of the diaphragm more typically than most patients, and she had symptoms of her chief complaint at the same time.

Case 27. R. S., male, aged 40, married.

Chief complaint: Tenderness in the epigastrium.

Present illness: The patient had epigastric pain first 10 years before entry, and his attending physician diagnosed peptic ulcer. The Sippy diet relieved his symptoms. Three months prior to observation he had recurrence of symptoms, and at this time a gastrointestinal series gave findings interpreted as duodenitis without gastric retention. He remained on the Sippy regime for three months and then began to have cramps in his legs, tightening of the muscles of his face and paresthesias of his hands. These symptoms happened under emotional strain.

Physical examination: Thin, asthenic male who appeared to be of the stated age. Hyperactive reflexes and 1° Chvostek's sign were found.

Hyperventilation exercise reproduced the symptoms of tetany. The patient was placed on ammonium chloride 0.6 gm. three times daily. He recovered from these symptoms, but in three months' time the symptoms of ulcer appeared. A neutral powder was then used so that the acid-base balance could be more finely adjusted.

Comment: It was felt that this man was on the verge of alkalosis tetany and in excitement mild over-ventilation caused the tetany to occur.

Case 28. J. C., female, aged 34, married (Case 1, Chart 1).

Chief complaint: Irritational distress in the epigastrium, duration 1½ years.

Present illness: This patient, a teacher, always had symptoms following the close of the school term. At these times she had epigastric distress, easy fatigability, headache, and paresthesias of the hands.

Physical examination: Negative except for hyperactive reflexes and Chvostek's sign 1° bilaterally.

Laboratory tests: The urine was alkaline; the blood was normal. See chart 1 for report of urine and blood chemistry.

Hyperventilation exercise produced headache, trembling of the arms and clonus, within nine minutes.

Progress: This patient improved markedly after acid therapy was instituted. Her neurosis was initiated by a marital problem which was later solved to some extent by her loss of symptoms and by an explanation of the problem.

Case 29. T. P., female, aged 31, married.

Chief complaint: Eructations of gas from stomach; and mucous colitis.

Present illness: For four years this woman had had increasing nervousness and irritability, and then she had midepigastric distress with eructation and nausea. Colitis with diarrhea developed and she expelled quantities of mucus.

Physical examination: A thin, poorly nourished, asthenic woman who talked so fast and inspired so rapidly that during the taking of her history she produced the symptoms of her complaint.

Laboratory tests: Normal findings for urine and blood. Gastric analysis: Absence of free acid in the fasting specimen and 32° after injection of histamine. Be-

fore hyperventilation, the urine tests by the Folin titration method showed 960°, and after hyperventilation 36°, which is evidence of a complete shift to "actual alkalosis."

Progress: This patient responded well to therapy directed toward production of mild acidosis. Her neurosis was based on the fear of losing her husband because of her chronic illness. This neurosis decreased with her improvement.

Group IX

Simulation of Diseases of the Special Senses

(*Pseudo-Mèniére's Syndrome*)

Case 30. T. M., male, aged 26, single (Case 9, Chart 1).

Chief complaint: Vertigo.

Present illness: This man had a sudden onset of dizziness and tinnitus with apparent loss of hearing in one ear, sometimes noticed on the left side, sometimes on the right. He noticed, also, a numbness of the hands with rigidity of the muscles.

Physical examination: The patient was of the pyknic type. At first the findings were normal save for hemorrhoids which were removed under general anesthesia. On return from surgery, he was in severe tetany with marked nystagmus, and while he was being revived by inhalations of CO_2 and injections of calcium chloride he again complained of tinnitus and deafness.

Laboratory tests: See chart 1 for findings.

Hyperventilation exercise reproduced in 12 minutes the symptoms mentioned above.

Progress: This man was placed on ammonium chloride, 0.6 gm. three times daily. When he was seen three months later, it was noticed that the exercise produced the symptoms after a longer interval from initiation of the breathing, and that the symptoms were not so profound. Later, after this man was married, his symptoms did not recur even when he was allowed a normal diet and when medication was withdrawn. Since this man was not the asthenic type, the true nature of his disturbance was not suspected until the symptoms occurred following the anesthesia. Other examples of this type of functional disturbance have been observed, and those patients have responded to the same measures.

Group X

Organic Disease (Coronary Occlusion) Producing Hyperventilation Tetany as a Symptom

Case 31. M. McM., female, aged 50, married.

Chief complaint: Spasms of the hands with hyperpnea.

Present illness: Patient had increasing fatigability and numbness of one hand and arm. Later, she had pain across the precordium. She had no dyspnea, orthopnea, palpitation or tachycardia. She began to have abdominal distention but did not have nausea or vomiting.

Physical examination: Heart was not enlarged to percussion. Sounds were very faint; they were regular and no murmurs were heard. Lungs were clear. Liver and spleen were not palpable. There was no edema.

Laboratory tests: Urine and blood were normal. The electrocardiogram showed left ventricular preponderance, diphasic T_1, slurred $QRS_{2,3}$, notched R_3, diphasic T_4, positive $S\text{–}T_1$, negative $S\text{–}T_3$.

Course: The day of entry she had an attack of distention, became slightly cyanotic, and had a definite carpopedal spasm. There was neither pain nor dyspnea. She was told to hold her breath, and without any medication the attack wore off quickly. The next morning she had another attack in which she died.

Comment: We mention this patient as an interesting example of the superposition of this syndrome on the symptoms of serious organic disease. This case in itself is a warning of the constant danger of classing too many patients as neurotic, and of the need for thorough physical proof to rule out organic illness before it is concluded that the patient's condition is merely a neurosis.

Group XI

Suspected Neuroses Which Were Not Proved by Hyperventilation Experiment

Case 32. L. P., female, aged 45, married (Case 5, Chart 1).

Chief complaint: Pain over precordium.

Present illness: This patient had attacks of weakness and dizziness which occurred at increasingly frequent intervals up to the time of entry into the hospital. Several months before, she had become conscious of pain over the precordium which did not radiate to the arms but which was associated with dyspnea and palpitation.

Physical examination: Sinus tachycardia was present. There was no evidence of myocardial damage.

Laboratory tests: Normal findings for urine and blood. Electrocardiogram, and roentgen-ray film of the chest for determination of the size of the heart, were negative. See chart 1 for reports of laboratory work after hyperventilation.

Hyperventilation exercise failed to induce the symptoms of the complaint, nor were symptoms of tetany produced. The CO_2 combining power was about the same as that found in other instances. She was placed on an acid-ash regime and improved as well as had other patients. It is probable that she was not exercised long enough to produce the desired results. Her neurosis was based on economic problems which were not solved.

Case 33. A. A., female, aged 43, single (Case 7, Chart 1).

Chief complaint: Precordial pain.

Present illness: Following the loss of her family, this woman had nervous irritability. Later she had pain in the left side of the chest, not radiating and not associated with dyspnea.

Physical examination: Negative.

Laboratory tests, including electrocardiogram, roentgen-ray studies of the chest and spine: No abnormal findings.

Case 34. R. McA., female, aged 40, single (Case 8, Chart 1).

Chief complaint: Hoarseness, duration 6 weeks.

Present illness: For 7½ years this woman had had pain in the tips of the fingers with skin lesions of a desquamating erythematous nature. She had also had numbness and stiffness of the fingers. She had had attacks of nausea and vomiting.

Physical examination: Skin lesions were present which are described above. Reflexes were hyperactive.

Laboratory tests: Urine and blood were normal. Electrocardiogram showed evidence of myocardial damage. Sedimentation rate: 35 minutes. No evidence of arterial disease was obtained by surface temperature readings before and after administration of spinal anesthesia. Response to alcohol meal was normal.

Hyperventilation exercise did not produce the desired results because of poor coöperation on the part of the patient on the several occasions when it was tried. It will be noticed that the CO_2 combining power increased; and this may be evidence that the patient became less sensitive to nervous stimulation.

Case 35. C. M., female, aged 51, widowed.

Chief complaint: Dyspnea, duration five years.

Present illness: Following the onset of irritability, this patient had dyspnea, and then precordial pain which was non-radiating in character.

Physical examination: Slight peripheral arteriosclerosis was present. The heart was not enlarged; a soft systolic murmur was heard at the apex.

Laboratory tests: Gastric analysis: No free hydrochloric acid even after injection of histamine. Electrocardiogram showed no evidence of cardiac damage. Roentgen-rays of the chest and gall-bladder were negative.

Hyperventilation exercise was not successful in producing the symptoms, chiefly because of inability to gain proper coöperation from the patient. She signed her release from the hospital before further studies could be made.

Comment: The patients of this group are presented to illustrate that the hyperventilation exercise, to be successful, must be performed when the patient is completely at ease and understands that coöperation is essential for the success of the experiment. It is possible that there are patients who will not react to the experiment even though they do coöperate. These may have other mechanisms which produce their neuroses or they may have organic disease, the symptoms of which are not affected by the irritating action of the hyperventilation exercise.

In table 1 are compiled the results of chemical studies on the urine and blood made before and after the exercise of hyperventilation.

It is to be noted that in only 10 of the 14 patients listed is the carbon dioxide combining-power shown to be reduced, as described by McCance and others.[2, 3, 11, 13] In all save two, the chlorides are increased.[13] The total calcium is normal, but in some instances the diffusible fraction is at the lower limits of normal. It may be that for these individuals, the diffusible calcium is actually below their normal threshold. Blood-sugar and serum-proteins are normal, but near the lower limits. Magnesium studies show normal determinations for most of the patients. In those in which the serum magnesium is low, the magnesium content of red blood cells offsets the effect of the loss of serum magnesium as a cause of tetany.[14] The most clearly demonstrable shift of pH is seen in the studies of the urine, in which the colorimetric readings show an increase of from 2 to 3 units. Likewise the drop in the ammonia per cubic centimeter is nearly 50 per cent. Acetone was found in only one of the specimens taken. It is felt that these results show a definite tendency towards alkalosis, and that the amount is that stated by Collip [2] to result in tetany. Because of the expense entailed in the complete analysis as given above, it was thought advisable to use a test which would demonstrate this change most simply and graphically. The Folin [15] pH titration method for urine may be used with good results. This procedure may be accomplished with the aid of the apparatus used in titrating gastric contents. With the addition of 15 to 20 gm. of potassium oxalate to 25 c.c. of urine, the titration is made with 0.1/N sodium hydroxide, using phenolphthalein as indicator. The specimens taken before and after the hyperventilation experiment are so tested, and are arbitrarily considered as being part of a normal output of 1,500 c.c. This step is made to take advantage of the normal figures as described by Folin, which

TABLE 1

Table of Laboratory Work on Patients with Hyperventilation Syndrome

Number	Patient	Social	Sex	Age	Neurosis	Symptoms	B. M. R.	CO_2 before HV (vol. %)	CO_2 after HV (vol. %)	Chlorides before HV (mg. %)	Chlorides after HV (mg. %)	Calcium (total)	Calcium (diff.)	Serum protein (total)	Serum albumin	Serum globulin	Blood sugar	Serum magnesium	RBC magnesium	Hematocrit	Urine pH before HV	Urine pH after HV	Urine ammonium total before HV	Urine ammonium total after HV	Urine ammonium per c.c. before HV	Urine ammonium per c.c. after HV	Urine acetone before HV	Urine acetone after HV
1	J. C.	M.	F.	34	Inheritance ? incapability	Weakness; dizziness; dyspnea; trembling	13.2 −	53.9	44.5	—	—	10.60	5.20	8.25	3.2	5.01	88	—	—	—	—	—	—	—	—	—	—	—
2	A. H.	W.	F.	38	Fear of advancing age; death of husband	Same as (1); tetany	—	48.5	42.0	—	—	10.50	—	—	—	—	—	2.2	—	—	—	—	—	—	—	—	—	—
3	C. C.	S.	F.	42		Same as (1); tetany	5.0 −	54.5	44.4	617	623	11.02	10.90	6.40	4 58	2.18	99	2.35	—	—	6.6	7.4	—	—	—	—	0	0
4	J. A.	M.	F.	32		Same as (1); precordial pain	7.6 +	53.8	44.4	594	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5	L. P.	M.	F.	45	Financial loss; ? home broken up	Same as (1); precordial pain; palpitation; tachycardia	3.0 −	48.5	44.7	605	594	10.12	9.92	—	—	—	99	2.5	5.2	42.8	—	—	—	—	—	—	—	—
6	D. E.	M.	F.	24	Divorce husband; indulgent mother	Same as (1); tetany; laryngeal spasm	—	—	—	—	—	8.67	4.62	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7	A. A.	S.	F.	43	Lack of family protection; not married	Pain in left precordium	—	57.8	52.1	596	612	11.12	5.5	—	—	—	—	2.2	6.85	43.5	—	—	—	—	—	—	—	—
8	R. M. A.	S.	F.	40		Same as (1); tetany; dermatitis fingers, toes	—	38.8	42.7	622	602	9.96	5.28	—	—	—	86	2.7	8.0	30.2	—	—	—	—	—	—	—	—
9	T. M.	M.	M.	26	Poor finance; fear of marriage	Same as (1); nausea; tinnitus; vertigo	20.7 −	52.2	56.9	599	562	10.35	5.00	5.70	3.82	2.05	89	1.95	7.25	42.5	7.2	9.1	23.0	12.2	.114	.091	0	0

TABLE 1—*Continued*

Number	Patient	Social	Sex	Age	Neurosis	Symptoms	B. M. R.	CO_2 before HV (vol. %)	CO_2 after HV (vol. %)	Chlorides before HV (mg. %)	Chlorides after HV (mg. %)	Calcium (total)	Calcium (diff.)	Serum protein (total)	Serum albumin	Serum globulin	Blood sugar	Serum magnesium	R.B.C. magnesium	Hematocrit	Urine pH before HV	Urine pH after HV	Urine ammonium total before HV	Urine ammonium total after HV	Urine ammonium per c.c. before HV	Urine ammonium per c.c. after HV	Urine acetone before HV	Urine acetone after HV
10	F. S.	M.	F.	27	Fear of husband	Same as (1); tetany; precordial pain; tachycardia	3.7 —	49.3	36.0	577	604	10.20	4.23	6.64	4.48	1.98	94	2.9	4.6	43.2	5.4	6.6	36.0	26.5	.40	.217	0	0
11	H.B.	M.	M.	27	Finance and mother-in-law	Same as (1); tetany	7.1 —	56.9	56.2	587	581	10.94	4.90	5.56	3.76	1.87	90	?2.25	?5.0	?14.5	5.4	7.6	75.8	32.5	.41	.22	0	0
12	F. H.	S.	M.	35	Finance	Epigastric pain; same as (1)	13.6 —	53.0	55.9	582	585	9.82	4.46	6.09	4.01	2.10	91	1.8	5.6	48.8	5.0	6.8	118.0	19.7	.62	.33	0	0
13	D. G.	M.	F.	35	? children	Same as (1); palpitation; tachycardia	5.7 +	43.6	48.3	584	582	10.30	4.92	5.35	3.86	2.26	98	1.7	6.3	45.7	4.8	8.0	40.7	11.2	.72	.22 —	0	0
14	C. D.	M.	F.	55	Incapability; told she was invalid by M.D.	Same as (1); laryngeal constriction (has myocardial damage)	20.0 —	60.6	53.1	594	617	10.00	5.33	6.09	3.79	2.28	99	—	—	—	5.8	6.8	19.6	3.64	.192	.113	0	0
15	M. M.	D.	F.	36	Nursed mother through anginal attack; demise of mother just prior to onset	General malaise; palpitation; dyspnea	8.4 —	58.6	38.6	—	—	10.70	—	—	—	—	—	—	—	—	5.4	6.2	—	—	—	—	—	—
16	M. M.	M.	F.	23	Death of father; birth of baby	Pain over precordium; dyspnea; tachycardia	9.8 —	50.1	42.6	455	418	—	—	—	—	—	—	—	—	—	acid	alk.	—	—	—	—	—	—
17	W. T. R.	S.	M.	27	Not determined	Pain in epigastrium; dyspnea and tension of facial muscles when talking	—	48.2	40.7	584	585	—	—	—	—	—	84	—	—	—	5.7	7.2	—	—	—	—	—	—

are 200 to 500° 0.1/N sodium hydroxide for that amount. Folin states that any figure under 250 is a good indication of actual alkalinity. So far, this test has proved satisfactory in that it shows a definite shift to "actual alkalinity."

Some explanation should be made for the almost insignificant changes in the figures which represent the shift in acid-base balance. In subsequent publications, Dr. Mayo H. Soley of our clinic and Dr. N. W. Shock of the Department of Biochemistry are to report the results of biochemical studies on similar patients, made in an attempt to gain more accurate data upon the rapidly changing shifts in the acid-base equilibrium and the gaseous exchanges through the lungs. They have found that the shift in pH of the blood is greater than has been indicated in the past, and that the reaction is a rapid one. They suggest that the indefinite results heretofore obtained are caused by the ungainly technic of venipuncture. The general trend of their results supports the contention that there is a definite alkalosis present when hyperventilation takes place.

In reviewing the histories of 50 patients, listed since 1928, in which the diagnosis of psychoneurosis with anxiety neurosis was made, figures were compiled which are shown in table 2. From the description of the

TABLE II

Since 1928, fifty patients have been admitted to the University of California Hospital whose conditions have been diagnosed as psychoneurosis with anxiety neurosis.

No. of patients with symptoms similar to the ones now described as associated with hyperventilation	36
No. of patients without these symptoms	14
No. of patients with the following symptoms:	
Weakness and fatigability	18
Numbness and paresthesia	14
Palpitation and increased cardiac rate	12
Dizziness	10
Nausea and vomiting	4
Muscular contractions:	
Twitching, trembling, convulsive states	14
Tetany (not on basis of hypoparathyroidism)	9
Difficulty in swallowing, talking, breathing (pharyngeal-laryngeal spasm)	8
Precordial pain (intercostal muscle and diaphragmatic spasm)	4
Dyspnea (diaphragmatic spasm)	14
Epigastric pain (diaphragmatic spasm)	2
Constipation (spastic colon)	5

The figures given above are compiled from the descriptions of the symptoms and signs that are given, and not from the results of formal experimentation.

symptoms and signs alone, nearly 70 per cent of the patients classed as psychoneurotic were found to have symptoms of hyperventilation tetany, either local or general.

DISCUSSION

In attempting to show the mechanism which is responsible for this sequence of events, we have constructed a diagram illustrating the physiological and biochemical changes which apparently form the background of

this disturbance. In chart 1, reading from the top downward, it is seen that the patient is presented with a problem the consideration of which causes fear. This problem is usually concerned with a social or an economic difficulty,—is usually in the realm of "romance or finance." The response

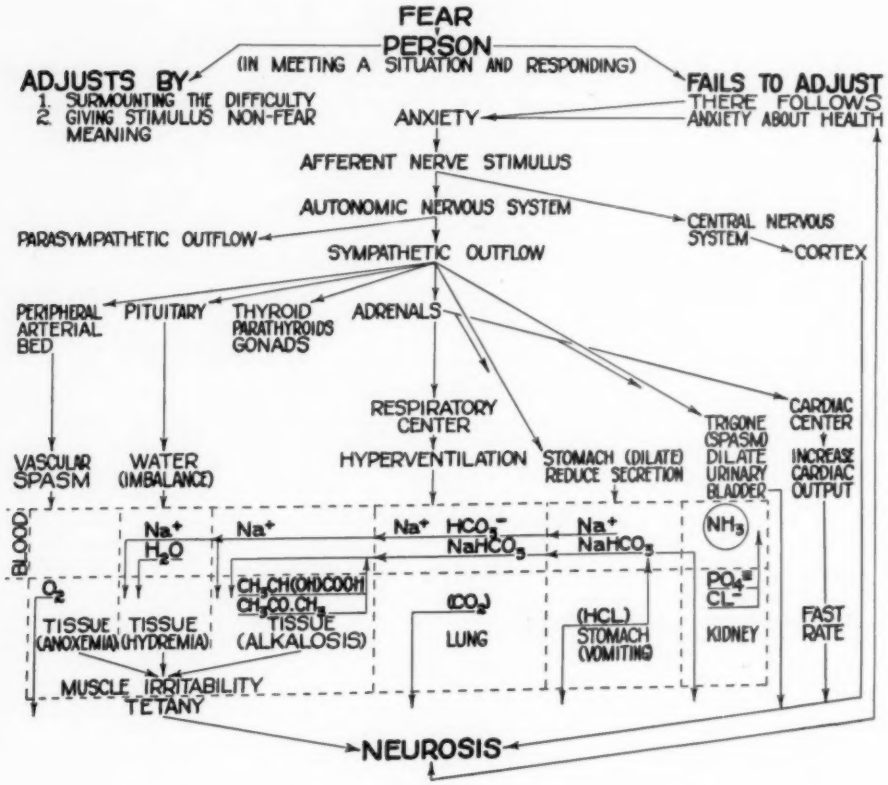

CHART 1.

in the average individual is ordinarily an adjustment which is made by solving his problem, or by neutralizing the fear that naturally arises by giving the problem a "non-fear" meaning. If some such adjustment is not made, the fear increases; and directly thereafter anxiety is manifested. Then the progression to a neurosis is but a simple process, and symptoms appear which cause the patient to feel ill. Anxiety concerning his health further aggravates the fear, and later the neurosis also. Hence the symptoms are increased. A variable period of time elapses until the autonomic nervous system is stimulated, in preparation for the unknown situation. The conventions of modern civilized life usually prevent the subject from fighting or running away from his situation. Thus the effective responses to emotional storms are blocked.

The chief response is through the sympathetic nervous system; the reaction of the parasympathetic system is less apparent.[16] Through the sympathetic system there is stimulation of the peripheral vascular bed, with spasm of the arterioles; and through impediment of the circulation a tissue anoxemia is produced which, according to Davies, Haldane and Kennaway,[17] causes increased muscular irritability, and thus increases the peripheral sensations. These authors have shown that this type of tetany can be relieved by oxygen inhalations. Bazett and Haldane[18] found that the hyperpnea due to hot baths can be relieved by a mixture containing 14.2 per cent oxygen and 8.5 per cent carbon dioxide. Hill and Flack[19] demonstrated that the hyperventilation of oxygen would not cause convulsions even when the alveolar carbon dioxide was reduced to 1.47 volumes per cent. Certainly tissue anoxemia is an exciting factor in the production of muscular irritability, and thereby it can produce tetany.

The stimulation of the members of the endocrine system is the second mechanism set in motion by the impulses coming in over the sympathetic nervous system. Stimulation of the pituitary gland has, for its chief effect, the reactions which follow increase in water retention by the tissues, with subsequent storage of sodium ions and production of alkalosis and tissue hydremia. The work of Furstenburg,[20] and, in an earlier period, of McQuarrie,[21] is mentioned here because of the low total protein and serum albumin which was found in all but one of the patients listed. This may be an indication of increase in hydremia, and if so there might be an increase in alkalosis through the presence of sodium ions.

The best known effect of the sympathetic stimulation upon the endocrine system is that of the adrenals. This stimulation, and the increase in the flow of adrenalin through the system, directly affects the substance of the nerves. According to Bonnet, Franck and Richard,[22] there is an increase in the summation of impulses, but no effect on the chronaxie of the nerve. With repeated stimulation, smaller impulses cause the discharge of the cycle of symptoms grouped as the complaints of these patients. Adrenalin is, of course, a cerebral cortical stimulant as well as a respiratory and cardiac accelerator by central action.

The stimulation from hyperventilation is most likely central in origin. Although no reports were found of studies in which adrenalin had been used, the work of Hammouda[23] throws some light on the question. This investigator found that, when he used heat as a stimulus, he was unable to produce panting in dogs by its application to any of the peripheral sensory endings in the rib-cage or its viscera. The only central nervous area that responded was the optic thalamus. Whether adrenalin acts at this point is, at present, a matter of conjecture.

A number of physiologists have studied hyperventilation in man. From the work of Collip and Backus,[2] McCann,[5] Grant and Goldman,[3] and from the observations reported in this paper, it is felt that the mechanism centers

chiefly in the $\frac{HCO_3}{NaHCO_3}$ buffer and its variations with the exhalation of carbon dioxide from the lungs. With this change, $NaHCO_3$ is left in the blood stream. This base is usually eliminated through the kidney, but the process is not fast enough to prevent some of it from being deposited in the muscle. In an effort to maintain the acid-base equilibrium, there is a reduction in the formation of ammonia [24]; hence less is excreted, as is shown in table 1. There is likewise a retention of phosphates and of chlorides.[11, 13] In all probability there is withdrawal of chlorides from the stomach for this purpose, which would explain the absence of free hydrochloric acid in the stomachs of these patients when tested. The muscles themselves add lactic acid to the equation. In some instances, acetone has been recovered [17] which is probably shielded by some of the alkali and excreted before normal oxidation can take place. Our findings are less constant in these respects than those of other authors.[2, 5, 11, 13] All of these attempts to acidify the tissues are insufficient, and the tissue alkalosis persists with subsequent hyperirritability of the muscles which finally leads to tetany.

According to Brody,[25] hyperventilation will definitely increase the irritability of the cortex, possibly because of tissue alkalosis. Brody feels that there may be some other factor as well. However, hyperventilation affects the patients described above in greater degree than it ordinarily does those people who overbreathe voluntarily. It is felt that this difference is due to the synergistic effect, described by Brody, occurring when hyperventilation is instituted after previous cortical stimulation from other sources. In such a state as that of fear or of any of the emotional reactions, adrenalin is probably the cortical excitant, instead of strychnine which was used by Brody.

The stimulation of the cardiac center by adrenalin causes an increase in the rate-volume output of the heart, after preliminary slowing of the heart due to an initial rise in blood pressure. However, when hyperventilation is present the results are more complex and somewhat more variable. McDowell [26] found that, when carbon dioxide is washed out of the blood stream by hyperventilation, there are two effects: (1) vasodilation due to central vasomotor control stimulation; and (2) vasoconstriction due to direct action on the peripheral vascular bed. In some patients the first mechanism seems to be in control; in others the second seems to predominate; and in still others there seems to be a balance, so that a variety of changes in the blood pressure and sensations due to change in the peripheral vascular bed may be predicted because of the variety of responses in adjacent areas. The important principle to remember is that this variety of reactions has the same cause, and can be managed according to the same regimen of treatment. Roome [27] supports the contention made by McDowell, and states that the addition of 5 per cent carbon dioxide to the inspired air will control these changes in the

peripheral vascular bed. According to McDowell, in animals this response is definitely attributable to a local chemical action and not to a nervous one, for there is no evidence of nervous stimulation such as dilation of the pupil or acceleration of the heart rate. However, in human beings there is little doubt, from the emotional nature of the onset of the disturbance, that the action of adrenalin is also a factor, and that the hyperventilation is more or less involuntary—at first as a natural sequel to the emotion. It is easy to see that local anoxemia may exist and be a factor in the cause of tetany. No studies have been made on the content of oxygen in the capillary blood supply to these regions, so that there is no definite proof of this statement. However, Striker, Goluben and Tarchanoff [28] have shown that alkalinization of capillaries by local application will cause constriction of the vessels of the bed. Severini and Krugh [28] stated that carbon dioxide will dilate the capillary bed. In cases of spasm, the constriction remains until muscle metabolites form to reduce the pH at that point, and then the spasm relaxes.

In connection with this syndrome, the presence of the symptoms of hyperthyroidism has been noted in patients seen in the authors' clinic. These patients have been treated by psychotherapy, and have improved. It is believed, however, that they suffer from this syndrome rather than from direct stimulation of the thyroid. There is no chemical evidence of any effect on the parathyroids. The stimulation of the gonads is a matter of conjecture. No observations on this subject have been made, although it is evident that work should be done. It is possible that in the sexual act, the orgasm is, in a sense, the result of hyperventilation tetany. In the process there is increase in the respiratory rate, increase in the irritability of the muscles that control the act of erection, and finally there is tonic spasm of the muscles of the sexual organs and of the skeletal system as well. How studies can be made under these conditions remains to be discovered; at any rate, the problem warrants consideration.

It is suggested by the work of Pottenger [16] that in addition to the suppression of free hydrochloric acid, dilation of the stomach and contraction of the sphincters would cause symptoms increasing the neurosis. The same is true of the effect on the urinary bladder, gall-bladder and renal pelvis in these patients who are really suffering from a form of sympathetic-cotonia. There is spasm of the internal sphincter and trigone, and dilation of the bladder. These symptoms, together with those resulting from direct cortical irritation, are sufficient to augment the neurosis; they cause the patient to feel ill, and thereby stimulate anxiety about his health—and the vicious cycle becomes complete. Repeated cystoscopy, or other local treatment, tends to augment changes in the mucous membranes and leads to further structural change.

It is well at this point to mention that another form of physiological disturbance has been observed in the psychogenic upset described above. Two patients were seen who had been so stimulated that hyperidrosis occurred

which was severe enough to cause a hypochloremia similar to that found by Piersol and Karr [29] in postoperative vomiting, in complications of peptic ulcer, and in hypertensive heart disease following the use of low salt diets. This portion of the subject is to be enlarged upon and reported at a later date.

The subject of seasickness, car-sickness (from riding in street cars, motor cars, and other rapidly moving conveyances), and air-sickness has attracted our attention over a period of several years. The close connection between the labyrinth, muscles of the eyes, and the gastrointestinal tract is well known. From personal observations upon many subjects in this group, it became apparent that anxiety is a significant factor in preparing the individual for the episodes which are so distressing to travellers. It is not assumed that certain subjects may not have over-sensitive labyrinths, or functional disturbances in the several structures participating in the production of these symptoms. However, the fact that most persons can become accustomed to the motions of conveyances, and the well known beneficial action of certain measures used in prevention and treatment (namely, sedatives such as bromides, antispasmodics such as atropine, peripheral dilators such as the nitrites, and inhalation of carbon dioxide) suggest that the anxiety state is more important than is generally appreciated. The termination of a bout of seasickness after several days may be promoted by the production of acidosis which compensates for the alkalosis induced by prolonged vomiting and anxiety combined.

Another problem—one which confronts those engaged in commercial conquest of the stratosphere—relates to altitude-sickness. Unless this problem is solved, the hazards of prolonged flight at altitudes above 12,000 feet will retard development. So far, attention has been centered chiefly in the reduced oxygen tension at high elevations. We proposed some time ago that a careful study be made of the concentration of carbon dioxide in the cabins of airplanes at these high altitudes. If ventilation is maintained and supplemented by oxygen and the carbon dioxide is lost, it would appear that subjects would suffer. Theoretically, if the respiratory mechanism is to function adequately, the carbon dioxide concentration should be kept at a higher level than normal. Experiments with this point in mind should be performed. The symptoms suffered by many of the subjects studied suggest a state of alkalosis.

The subject of hysteria is of historical and practical interest. It is our opinion that theoretically the episodes can in many instances be explained by the presence of the anxiety state, with extreme effects upon the psyche and periphery. The stocking-and-glove anesthesia is more likely a disturbance caused by limitation of the blood supply to the peripheral nerves, than due to central effects upon the peripheral nerves themselves. One cannot exclude blocks in the somatopsychic pathways wherein the registration of sensation from the periphery is wanting.

Treatment

Treatment of patients suffering from this condition should be divided into two types: palliative and curative. The latter procedures consist of the use of psychotherapy by such means as psychocatharsis, reëducation, reassurance, and the substitution of a " non-fear " meaning in situations where desensitization is needed. The palliative measures or medicaments have very definite use for several reasons. Through immediate relief of symptoms, part of the cause of the neurosis is removed—namely, that portion dealing with the patient's concern regarding his health. He feels well for the first time in months, and therefore the emotional rapport with the physician is made stronger, so that the psychiatric procedures mentioned above may be performed much more easily. Also, the demonstration illustrates to the patient the mechanism of the physiological difficulties which he himself has caused, and the results are so dramatic that he is able to follow the procedure and to appreciate what the results mean to him. He is then in a position to check the physical changes at an earlier period, and to save himself from more profound disturbances.

The use of any agent that will break the course of events described in chart 1 will accomplish this purpose. The first group of measures are those which help to control the acid-base balance. These were used in the patients of our series. The inhalation of oxygen-carbon dioxide gas (70 per cent O to 30 per cent CO_2) is most effective [30] both in speed and adequacy. When the apparatus is not at hand, a paper sack inverted over the patient's head and sealed with adhesive tape, is successful. Some patients have responded to drinking small quantities of carbonated water or beer. Although these methods work well in convulsive attacks, it is found of advantage also to place these patients on an acid-ash diet; to reduce the fluid intake to 500 c.c.; and to administer ammonium chloride in dosage [30, 31] as large as one gram, given by mouth in capsules from three to six times a day. A suitable prescription is as follows:

Ammonium chloride	30.0
Fld. ext. licorice	20.0
Syr. yerba santa	75.0
Cinnamon water q. s. ad	120.0

Sig.: One teaspoonful 3 to 6 times per day.

Or, simply the use of the Mistura *glyccerhizae co.* as the vehicle is successful. Chloride ions may not be as effective as carbon dioxide for Douglas and Havard [30] have shown that carbon dioxide permeates the respiratory center more quickly than chloride ions.

The next two methods are projected for future work. The first of these is based on the work of Levy and Ditz [32] whose studies were limited to the phenoxyethylamine and orthomethoxyethylamine compounds. They tested the action of drugs in these groups on the heart action and respiratory rate in dogs; on the intestine *in situ* of the dog; and on the isolated intestine of

the guinea pig. They followed the metabolism of the glucoside in the rabbit, and the toxicity by intravenous route in the mouse. Of the group of eight drugs, there is one that will prevent vasoconstriction, inhibition of intestine, and increase in the respiratory rate—and that compound is *phenoxylethanolamine 2 ethane.* This preparation has to be given prior to the expected extravasation of adrenalin, and is really preventive rather than curative. So far as is known, this group of drugs has not been used in the treatment of human beings. Other better known drugs have been used: these are ergotamine, yohambin, hydrastin and quinine. Their use is preventive also.

Another method is suggested by Pottenger's reports.[16] After proving, by the tests he has outlined, that a patient is sympatheticotonic, one might endeavor to develop parasympathetic tone in opposition to the former state. Pilocarpine, histamine, and acetylcholine are suggested by this author as a means of attempting to convert these people to a more median type. A difficulty arises here because some people have excess in both systems, and this method would aggravate symptoms of parasympathetic tone which do not form a part of the picture described above.

Summary

The authors believe that there is a physiological background for the perseverance of an anxiety state as part of a psychoneurosis; that this background is produced by the constant presence of purely emotional disturbances; and that the resultant physiological state aggravates the psychic component to such a degree that a vicious cycle is instituted, the symptoms of which are manifold. These symptoms increase the severity of the emotional tension; and, if they are prolonged, permanent structural change with the production of organic disease results.

The mechanism is at first a repetition of attacks, from the stimulation by an emotion such as fear upon the sympathetic nervous system, which in turn becomes increasingly labile. The mechanism is perpetuated by the effects of the stimulus on the system of self-defense, which is dispatched by the endocrine group. This reaction causes a state of hyperirritability to exist through the presence of tissue alkalosis, tissue hydremia, and tissue anoxemia; and results in a state of tetany which may be regional or generalized.

The symptoms of tetany, and allied manifestations such as tachycardia, distended stomach and dilated urinary bladder, are enough to aggravate the neurosis because of the patient's fear of impending dissolution. Multiplication of impulses increases the bombardment of the sympathetic nervous system, making repetition of the reaction more easy at subsequent intervals.

The cure is accomplished through elimination of the fear-impulse by psychotherapy. The symptoms may be alleviated medically, and by this means that part of the neurosis which is on the basis of anxiety concerning health may be eliminated. Because of the subjective and objective improve-

ment in the patient's condition, contact for psychotherapy is more easily obtained. Medical treatment is directed toward preservation of the acid-base balance; toward decreasing the effect of adrenalin on the nerve-tissue by means of a known chemical antagonist; or toward converting the state of tone of the individual from extreme to moderate, whether parasympathetic or sympathetic in type.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

RECTAL STENOSIS FROM ROENTGEN THERAPY: REPORT OF TWO CASES*

By T. Grier Miller, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

The simultaneous occurrence under my immediate observation of rectal stenosis following roentgen therapy in two patients with carcinoma of the prostate has served to emphasize a significant hazard in the radiation treatment of various pelvic lesions. The complication apparently is well recognized by gynecologists, proctologists and radiologists, but internists generally have not fully appreciated its frequency or clinical importance. In one of the cases which I shall report a colostomy was required and in the other, it was under consideration when uremia, as a result of bilateral ureteral obstruction from secondary carcinomatous involvement, supervened and caused the patient's death. In each of them a diagnosis of rectal irritation from roentgen exposure was made early in the course of the therapy and in each, ultimately at autopsy, an intense fibrosis of the rectal wall with narrowing of the lumen was demonstrated.

An important report on the type of the rectal lesion produced by radiation and on its symptoms and diagnosis has recently been presented from this hospital by Ferguson.[1] He has also reviewed the literature and given certain clinical and laboratory data on eight cases personally studied: six, irradiated for carcinoma of the cervix; one, for carcinoma of the urinary bladder, and one, for carcinoma of the prostate. I wish somewhat more fully to trace the development of the lesion in my two cases and to emphasize its relation to undesirable radiation effects in other parts of the body.

Case Reports

Case 1.† M. J. G., a physician of 72 years, who had first consulted me 17 years previously because of a transient attack of kidney colic, due to the passage of a small calculus, and subsequently from time to time for minor arthritic symptoms, complained in August 1934, of bladder irritation. He was able to void only 35 c.c. of urine at a time. I found his prostate enlarged and indurated. Three competent urologists‡ considered that the left lobe contained a malignant lesion and that the case was inoperable. Roentgenological study of the bones was negative for metastases. Roentgen therapy was decided upon.

The first series of treatments§ was begun on August 22, 1934 (see table 1 for details of total roentgen therapy). On October 30, one of the urologists (Pelouze)

* Received for publication August 16, 1937.

From the Gastro-Intestinal Section of the Medical Clinic, Hospital of the University of Pennsylvania.

† Included in Ferguson's series of 8 cases.

‡ Dr. P. S. Pelouze, Dr. S. W. Moorhead and Dr. Alexander Randall.

§ The roentgen therapy in these cases was given by Dr. E. P. Pendergrass and Dr. G. W. Chamberlin of the Radiology Department of this Hospital.

TABLE I

Details of Roentgen Therapy in Cases 1 and 2 *
(Data submitted by Radiology Department)

Date	Portals	Dosage	
		Each	Total
Case 1		r	r
Aug. 22–Sept. 19, 1934	2 anterior pelvic	1845	3690
	2 posterior "	1845	3690
			7380
Nov. 19–Dec. 21, 1934	2 anterior pelvic	2000	4000
	2 posterior "	2000	4000
			8000
May 13–June 17, 1935	1 posterior pelvic	2025	2025
	1 perineal	1350	1350
			3375
Dec. 12–Jan. 17, 1936	2 anterior pelvic	2000	4000
	2 gluteal	2000	4000
			8000
Case 2		r	r
May 22–June 15, 1935	2 anterior pelvic	2000	4000
	2 posterior "	2000	4000
	1 perineal	800	800
			8800
Oct. 31–Dec. 4, 1935	2 anterior pelvic	2000	4000
	2 posterior "	1838	3676
	2 gluteal	1000	2000
	1 perineal	2000	2000
			11676

* Irradiation factors: 165 K.V.; constant potential; 15 ma.; 50 cm. distance; 2 mm. Cu. or Thoreus filter equivalent to 2 mm. Cu. All measurements are as in air.

reported marked diminution in the size of the prostate but persistent induration; by that time the patient was passing as much as 110 c.c. of urine at a time. Toward the end of the second series of treatments he developed, in addition to subcutaneous edema of the lower abdomen, some diarrhea and bladder irritation, recognized as due to the radiation, but the latter phenomena soon subsided and his urinary output at a single voiding amounted to 260 c.c. His urologist then reported that the gland was little above normal in size and that the mass, previously felt in the left lobe, had disappeared. He stated, furthermore, that had he not seen the patient before he could not then have diagnosed the presence of a malignant lesion.

Soon after the third series of treatments (given May to June, 1935) he began to pass mucus by bowel and to have much rectal irritation. On October 8, a barium enema study showed marked narrowing of the lumen of the rectum, sigmoid and descending colon. Cystoscopic investigation showed an elongated posterior urethra

with a definitely raised bladder neck and 175 c.c. of residual urine; the prostate itself still was not very large. A trans-urethral resection by Dr. Randall was done on October 18, after which he again became asymptomatic and was able to go back to his work. On December 10, his residual urine was only 10 c.c.

Subsequent to the fourth and final series (given December 1935 to January 1936) he seemed in excellent general condition, and on March 14, Dr. Randall reported that his prostate showed only a little deep induration and some slight fixation. On June 20, he again reported on the prostate as follows: "flat, much softer than heretofore, rather finely nodular and not sensitive; residual urine 30 c.c."

In August, however, he complained of marked rectal pain, tenderness and bleeding, with bouts of constipation and spasmodic pain on attempts at defecation, for which I referred him to a proctologist (L. K. Ferguson). He found marked edema and hypertrophy of the wall of the rectum and capillary bleeding from the mucosa on the slightest trauma, effects which he unhesitatingly attributed to the irradiation.

With astringent applications and a non-residue diet the rectal symptoms subsided, but during September another trans-urethral prostatic resection was necessary. Again he returned to his work and felt reasonably comfortable, but by December 1, he had developed additional edema and marked capillary dilatations of the lower abdominal wall and had some incontinence of urine alternating with retention which required catheterization. At the same time his stools were beginning to be of small caliber and ribbon-like; sometimes he had fecal incontinence. I found, on digital examination, an annular mass in the rectum with marked constriction of the lumen, which I at first thought was due to a malignant rectal lesion. By December 28, however, the rectal wall was less indurated and a finger could pass through it, as though the stenosis were due merely to edema of the wall.

In spite of this, on January 4, 1937, Dr. Randall reported improvement in his local condition with "softening of the prostate and surrounding tissues; no fixation or stony hardness; residual of 30 c.c."

On March 10, he complained of a feeling of obstruction in the rectum and was unable to secure even a small liquid evacuation without a strong laxative. He was moderately anemic and emaciated in appearance, though his weight, because of the edema about the lower abdomen and back, was as usual. Again a rectal mass was palpable, but the proctoscope revealed only edema.

On April 3, he was admitted to the hospital because of marked abdominal pain and distention, fever and inability to evacuate the bowel. Rectal obstruction, due to edema and fibrosis of the bowel wall from radiation, was diagnosed. A catheter, however, could be passed slowly through the constricted area of the rectum, but only a small amount of fecal material could be washed out. Intubation of the small bowel from above allowed the escape of much gas and fluid with relief of the distention. A large mass was then felt in the right kidney area. A colostomy was considered, but he promptly became anuric, his urea nitrogen concentration rose to 140 mg. per cent and he died April 7, 1937.

Autopsy revealed a primary carcinoma of the prostate with secondary involvement of the urinary bladder, chiefly about the trigone and the ureteral orifices, and bilateral pyonephrosis. The rectum itself was not involved in the malignant process, but, according to the pathologist (O. N. Smith) "in the rectum, beginning about 3 cm. from the anal orifice and extending proximally for about 12 cm., there was a brawny thickening of the wall, most conspicuously involving the muscularis and simulating the hypertrophic changes seen in pyloric stenosis. This markedly constricted the caliber of the lumen, so that the index finger could be passed only with considerable force. Although the rectum was adherent to the posterior surface of the bladder, the diffuse involvement of its wall was not grossly neoplastic." Dr. Morton McCutcheon reported on his microscopic study of the sections as follows:

"There is marked chronic proctitis, characterized by mucosal destruction and by submucosal edema, fibrosis and inflammatory exudate. The inner muscularis is markedly degenerated, vacuolated with fat, and conspicuously replaced by fibrous tissue. Several arterioles are markedly hyalinized. The outer muscularis is less damaged. The fibrosis and muscular degeneration are much more marked in the rectum than in other sections of the sigmoid, small intestine and stomach."

Comment on Case 1

It will be noted that following the second series of treatments, and about four months after the beginning of radiation, diarrhea was first observed. Following the third series, five months later, he was passing much mucus by rectum and about one year after the first radiation a barium enema showed marked narrowing of the lumen of the rectum, sigmoid and descending colon. Again, however, he became asymptomatic, and in spite of the necessity for a prostatic resection (to relieve bladder retention) and a fourth series of roentgen treatments, he had no further significant rectal symptoms until August 1936, two years after the first treatment. Then he was proctoscoped for the first time and the examination disclosed rectal edema, hypertrophy of the wall and capillary bleeding. In spite of these local phenomena his rectal symptoms again subsided temporarily, but four months later he became constipated, had spasms of pain on defecation and the stools, when formed, were ribbon-like in character. Digital examination showed marked narrowing but the finger could be introduced slowly, apparently as the edema was reduced by pressure. This observation was subsequently confirmed by the proctoscope. Autopsy four months later, however, showed not only edema but true fibrosis of the wall.

Thus it seems clear that, although early he developed some irritation of the rectal wall, it was transient as also was some of the edema that occurred later, and not until after almost two and a half years did he develop the true fibrous and stenotic lesion which was found at autopsy.

Case 2. E. M., male, 72 years of age, a business man with large responsibilities, was referred to me by Dr. Isaac W. Kingsbury, of Hartford, Conn., on March 8, 1935, complaining of epigastric discomfort, relieved by alkalies, and of attacks of substernal distress with reference into the left arm after physical and mental strain. He was of the tall, thin, duodenal ulcer type; obviously arteriosclerotic; had systolic murmurs at the apex and base of his heart but no enlargement, and a blood pressure of 130 systolic, 85 diastolic. His prostate was moderately enlarged and firm. Urine, blood and stool examinations were negative. Free hydrochloric acid was present in excess in his gastric contents. An electrocardiogram showed some extrasystoles and evidence of myocardial damage. Gastrointestinal roentgenological study revealed a large active duodenal ulcer.

On May 17, 1935, Dr. Alexander Randall found characteristic evidence of prostatic malignancy. Roentgen study of the bones showed no metastases. Roentgen therapy was started at once (table 1). After the first series of treatments the prostate was much improved: smaller, more elastic and less nodular. Meanwhile he had developed some nausea and vomiting and had lost some weight (from 169 to 160 pounds). His ulcer symptoms had subsided and he had no more disturbing cardiac

attacks. Subsequently (July) some irritation of the skin in the hypogastrium developed and he had some frequency of bowel evacuations and irritability of the urinary bladder. On July 12, another gastrointestinal roentgen study showed the duodenal ulcer defect still present but associated with less spasm.

He had regained his usual weight by October and was in good general condition, but the left lobe of the prostate was larger and firmer. A second series of roentgen treatments was begun, and in the midst of that he developed marked edema and irritation of the lower abdominal wall, the buttocks and the perineal region. On completion of the series, however, the prostate seemed smaller and less hard. Again he had lost weight but, except for the skin lesions, one of which had ulcerated, was in good shape. Some fecal incontinence developed a few weeks later and the urinary bladder again became very irritable.

By January 27, 1936, he had regained his weight and the skin condition had improved though some hard edema persisted. He was able to go through the night without voiding.

On his return, in April, from a trip to the west coast, where he played as much as 12 holes of golf without incident, he had no special complaints, but his prostate was a little larger and seemed fixed to the bone on the left side. A month later he had some leg pains, suggestive of bone metastasis, but roentgenological examination was negative. On the basis of special vascular tests it finally was decided that the pains were on an arteriosclerotic basis and some "suction and pressure" therapy was given.

Prostatic examination by Dr. Randall, on September 24, revealed no new developments, but again he was having marked bladder irritation with nocturnal frequency. Shortly afterwards he developed a recurrence of the fecal incontinence. On November 25, he was complaining of stiffness in the loins and above the iliac crests but no abdominal masses could be felt. Edema of the groins and perineum was still marked. On December 18, he developed suddenly left chest pain and hemoptysis which suggested a pulmonary infarction, but roentgen study of the lungs showed only thickened trunk shadows, and he had subsequently no recurrence of the pain or hemoptysis. At the same time he developed some pain in the lower abdomen and back, but it was not persistent.

On April 17, 1937, he was complaining particularly of fecal incontinence, especially on urinating, alternating with constipation for 3 or 4 days. Blood frequently appeared in his stools. His appetite was impaired and he was losing weight (152 pounds). His sigmoid was full and doughy. On rectal examination marked edema of the wall with narrowing of the lumen as far as one could reach was found, and above that a mass in the lumen, probably fecal. Anteriorly through the edematous wall marked induration could be detected and a spreading prostatic lesion was suspected.

A week later he was again referred to the hospital because of abdominal pain, failure to evacuate the bowel and a suspicion of intestinal obstruction. The lower abdomen was tense and sore. Digital examination of the rectum showed diffuse induration but a smooth wall. A finger could barely be inserted. Finally a urethral catheter was slowly passed for 10 to 12 inches into the lower bowel and through that much blood and fecal material were evacuated, as a result of which he became quite comfortable. That procedure was repeated several times, but finally the results were unsatisfactory; and on April 30, a colostomy was performed by Dr. E. L. Eliason. The patient was quite alert after the operation for two hours, but then rather suddenly became distressed, cyanosed and dyspneic, developed a leaky skin and feeble pulse and died.

Autopsy by Dr. O. N. Smith showed that death had resulted from complete occlusion of the left coronary artery, already extensively sclerosed and calcified.

The prostate was only slightly enlarged and without induration suggestive grossly of carcinoma, but in the left lobe was a mass of gray tissue, 1 cm. in diameter, which microscopic study showed to be malignant. The rectum was markedly compressed by a mass of carcinomatous tissue which lay between it and the sacrum. The urinary bladder and ureters were not involved, but the lymph nodes along the abdominal aorta, about the head of the pancreas and those situated extraperitoneally in the pelvis were massively implicated. The sigmoid was adherent to the peritoneum below the pelvic brim and the upper rectum was more or less encased in carcinomatous tissue. The rectal mucosa, however, was not carcinomatous, but it was infiltrated with round cells and polymorphonuclears. The submucosa was edematous and fibrotic. The muscular cells were vacuolated and degenerated. The perimuscular adipose structure was infiltrated with fibrous tissue and edematous, and it contained an occasional metastatic carcinomatous mass, the result of lymphatic spread. The lungs showed metastatic lesions. The duodenum showed a small healed ulcer and the liver, multiple cysts, one of which contained 600 c.c. of fluid.

Comment on Case 2

The obstruction in this case obviously was due in part to the metastases which surrounded the rectum, but also in part to the edema and fibrosis of the rectal wall. The fact that a finger could be inserted into the lower rectum only very slowly, seemingly displacing fluid from the wall as it passed, and that a semi-rigid rubber tube could be introduced only in the same way left no doubt in the mind of the examiner that he was dealing with stenosis due to edema. The observations at autopsy, furthermore, indicated that the compression of the rectum by the metastatic lesions was not sufficient in itself to produce complete obstruction.

In this case also it will be noted that irritation of the rectum, indicated by diarrhea, occurred soon, about two months, after beginning radiation therapy, but was transient. Fecal incontinence came on after the second course of treatment, but that also subsided within a short time. It recurred, along with bladder irritation, however, after another year and then persisted until he developed definitely obstructive symptoms. Unfortunately no proctoscopic study was made in this case, but the frequent presence of blood in the stools suggests that, in addition to edema of the wall, telangiectatic areas, such as have frequently been demonstrated in other cases, were present.

General Discussion

The intimate anatomical relationship of the rectum to the urinary bladder, the prostate and the cervix of the uterus accounts for its involvement when any of these organs is subjected to intensive radiation therapy. Although the portal of entry of the roentgen-rays through the skin may be altered from time to time, it is impossible to direct the rays so as to avoid almost maximal exposure of the deeper tissues in the immediate neighborhood of the lesion under treatment. The skin reaction, therefore, cannot be a measure of the effect produced internally on adjacent structures.

That intensive radiation is capable of producing irritating and eventually destructive effects elsewhere in the digestive tract is well ap-

preciated. Desjardins [2] has reviewed the literature in reference to its action in the mouth, where in overdosage it produces ulcerative lesions, permanent telangiectases and serious dental disturbances; to its destructive action on the salivary glands; to the degeneration of epithelium, hyperemia, hemorrhage, atrophy and fibrosis which occur in the stomach, and to the mucoid degeneration, hyperemia, edema, ulceration and fibrous tissue replacement that take place in the small intestine. Nelson and Hirsch,[3] in reporting a case treated for suspected malignancy of a cervical lymph gland, state that the autopsy showed severe necrosis and scarring of the pharynx, larynx and upper parts of the trachea and esophagus. Schenck [4] has repeatedly observed irritation and edema of the larynx in patients given roentgen therapy for hyperthyroidism. Elliott and Jenkinson [5] had a patient who died as a result of intestinal perforation secondary to ulceration from roentgen therapy for abdominal Hodgkin's disease.

Irritation of the urinary bladder, such as occurred in both of my cases, has been more often reported as a result of radium treatment for carcinoma of the cervix, but roentgen therapy also has been employed in most of these cases. Everett [6] refers to 18 cases, so treated, 7 of whom eventually developed a vesico-vaginal fistula and 11, bilateral ureteral stricture. Dean [7] has studied 47 women for lesions of the bladder incident to radiation therapy: cystoscopic investigation, on an average of two and a half years after the therapy, showed ulceration and anemic areas surrounded by intense inflammation or punctate hemorrhage. He stated that these lesions might follow comparatively light applications of irradiation.

The incidence of rectal complications of radiation therapy is indicated by Buie and Malmgren's [8] statement that in 2,073 cases subjected to pelvic irradiation for extra-rectal lesions they found 3.13 per cent that had rectal symptoms and a lesion discoverable by the proctoscope. The onset averaged 11.6 months after treatment and the outstanding symptoms were bleeding, pain, diarrhea, urgency and tenesmus. The proctoscope invariably showed telangiectases and bleeding. Ulcers were present in 43 per cent of the cases.

In a series of 520 cases of cervical carcinoma treated by irradiation eight months to eight years previously, Jones [9] found seven instances of benign stricture of the intestine, although none of them had received excessive dosage according to present standards. Only one had the stricture in the rectum, but five in the sigmoid. The lesion in all instances was an annular fibrous thickening, localized and obstructing the bowel. Newell and Crossen,[10] in a series of 371 irradiation cases, had five with rectal stricture, but all were of slight degree and satisfactorily treated by dilatation.

Jones,[11] Ferguson [1] and other authors have recognized early and late phases of the rectal reaction to radiation: the one occurring within a few weeks or months after treatment; the other, months or years later. Jones, whose observations were made on women with cervical carcinoma who received radium, stated that a dose sufficient to cure the lesion would produce erythema of the rectum and that the early symptoms of the latter were a

burning sensation and frequency of defecation, while later, after six to eight months, in the more severe cases, marked pain and tenesmus with blood and mucus might develop. Ferguson, whose experience has included patients treated not only with radium but also only with the roentgen-ray emphasizes the severity of the early symptoms chiefly in the radium cases. This seems reasonable since they receive a larger dosage of irradiation at one time. In neither of my cases was anything more than a slight and transient diarrhea, with the occasional passage of mucus, noted in the first phase of the reaction. In spite of this, both eventually, after an interval of freedom, developed the characteristic late symptoms: spasms of pain on attempt at defecation, diarrhea alternating with constipation, marked tenesmus and bleeding with and after each bowel movement. On two occasions in one of the cases a proctoscopic examination, made late in the course of the illness, revealed a contracted, edematous and bleeding rectal wall. The other case was not proctoscoped, but in both, the autopsy findings demonstrated clearly the presence of marked edema and fibrosis producing stenosis. Telangiectases were not observed, but since they have frequently been described in such cases it is to be assumed that they were present and accounted for the bleeding.

Conclusion

Two cases of stenosis of the rectum, due to intensive radiation therapy for carcinoma of the prostate, are presented in order to call attention to its occurrence. Although in each of these cases the malignant lesion had not been eradicated by the radiation and early death was inevitable, it is believed that the recognition of such rectal stenosis in certain other patients, in whom the primary lesion is under control, may lead to appropriate surgical therapy and be life saving.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

PANCREATITIS AND DIABETES *

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THE involvement of the pancreas as a cause for diabetes is, to a great extent, taken for granted. The exact changes in the pancreas responsible for the development of diabetes are not clearly defined. The situation is a good deal as though all pulmonary conditions—tuberculosis, the pneumonias, abscess, bronchiectasis, asthma, passive congestion—were classified as a disease entity characterized by expectoration and all treated alike on that basis.

Certain phases of pancreatic pathology—carcinoma, cyst, adenoma—are well established, but the lesions resulting in diabetes are not satisfactorily evaluated. An attempt will be made in this paper to correlate the changes in the pancreas with the various manifestations characteristic of diabetes. The gradual development of knowledge in regard to the anatomical and the functional pathology of the pancreas warrants an effort of this sort at the present time, though the conclusions reached are tentative only and await further clinical and laboratory data for their elaboration.

PATHOLOGY OF THE PANCREAS IN DIABETES

An involvement of the majority of the islands of Langerhans causes diabetes; the pancreatitis resulting in such lesions may be chronic or acute, permanent or transient.

CHRONIC PANCREATITIS

Chronic pancreatitis develops in elderly persons because of arteriosclerosis and senescent processes. This form of chronic pancreatitis may be regarded as primary chronic pancreatitis. When the chronic pancreatitis is the sequel, through scarring, resulting from an acute pancreatitis or from pancreatic duct obstruction, it may be considered as secondary chronic pancreatitis.

PRIMARY CHRONIC PANCREATITIS

This type of pancreatitis results in the slowly progressive form of diabetes which occurs in late middle life and in old age; it is generally known as the essential diabetes of Naunyn, and should be ascribed to the degenerative changes incident to advancing years. It should be sharply distinguished

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from the forms of diabetes characterized by exacerbations and found in younger individuals.

Warren calls attention to the occurrence of three predominating lesions in the islands of Langerhans in his series of 259 diabetic pancreases, as follows:

Total Number of Cases—259

Normal	69
Fibrosis	69
Hyaline	89
Hydropic degeneration	15

The above tabulation furnishes data only in regard to the qualitative changes in the islands of Langerhans and gives no information about a diminution in their number. It may very well be that in the group designated as normal, a number of islands have disappeared and left no trace which can be identified under the microscope.

Hyalinization of the islands of Langerhans occurs almost entirely in persons over 40 years of age; it is also found in non-diabetics. Fibrosis, like hyalinization, is more frequent in older individuals and yet, though common, is not often mentioned as a cause for diabetes. Joslin subscribes to the idea that fibrosis of the islands is nearly as common a finding as hyalinization. Fibrosis and hyalinization of the islands may appear in the same pancreas and the two lesions may even be combined in the same island. It is tempting to assume that both fibrosis and hyalinization of the islands are part of the aging process and the arteriosclerosis incident to human existence.

Secondary Chronic Pancreatitis

Secondary chronic pancreatitis results from destruction of the pancreas brought about by obstruction of the pancreatic ducts, through pancreatic calculi or external pressure, by acute pancreatitis, and by pancreatic cysts or hemorrhage within the pancreatic tissue. The subsequent development of diabetes depends upon the number of islands of Langerhans which are destroyed. Very frequently, probably in most cases, too few islands are involved to result in diabetes. Especially noteworthy in this connection is the experimental observation of MacCallum that after ligation of a pancreatic duct, all the corresponding pancreatic tissue atrophies, except the islands of Langerhans, which are preserved; this has been verified in human beings with long standing obstruction of the pancreatic ducts.

The diabetes resulting from secondary chronic pancreatitis is usually mild and non-progressive (see Case 5) unless there is a recurrence of the process which extends the involvement of the islands of Langerhans.

Acute Pancreatitis

Fitz in 1889 designated the varieties of acute pancreatitis as hemorrhagic, gangrenous and suppurative; while these three types of injury are

still recognized they have come to be regarded as parts of the same process, that is: acute pancreatitis (Pratt, Warfield, MacCallum and others). Pratt says: "The subdivisions made by Fitz into hemorrhagic, gangrenous and suppurative forms of acute pancreatitis represent different stages in the same pathological process which begins with necrosis of the pancreas." This severe form of acute pancreatitis, characterized clinically by marked epigastric pain, shock and collapse, was the only one recognized for a long time and is the only one considered by many clinicians today.

Pratt was one of the first to describe the mild cases, differing largely from the severe cases in that a smaller amount of pancreatic tissue was involved. Since then, Warfield; Dragstedt, Haymond and Ellis; and Rich and Duff, have made the same observation. Such minor involvements of the pancreas according to all these observers are frequently found. The turbulent course of diabetes in the young is probably due to recurring attacks of this sort. The rarity of acute pancreatitis, as stressed by Root, would consequently apply only to the severe form and not to the milder, nonfatal attacks.

The etiology of acute pancreatitis has been a matter of considerable debate. The majority of authors specify diseases of the gall-bladder as being primarily responsible. Dragstedt, Haymond and Ellis, in an intensive study of this problem, come to some very important conclusions. Edema and hemorrhage of the pancreatic parenchyma are frequent findings; they constitute milder attacks of pancreatitis, which may develop into necrosis, limited or extensive, that is, the significant change of severe acute pancreatitis. These authors believe that bile, and infection by *B. welchii* are the separate determining factors in bringing about the necrotic process. (This is in contrast to the opinion of others, e.g., Rich and Duff quoted subsequently.)

According to Dragstedt, Haymond and Ellis, it is probable that approximately 60 per cent of the cases of acute pancreatitis in man have developed as a direct result of the passage of bile into the pancreatic ducts; the causes of the pancreatitis in the remaining 40 per cent are: (1) extension of infection via the lymphatics from an infected gall-bladder or neighboring viscus; (2) trauma; (3) hematogenous infection, as in mumps; (4) stasis of the pancreatic juice—plus infection; (5) reflux of the duodenal contents into the pancreas.

Rich and Duff, from their experimental and pathological studies, develop the idea that the main cause for acute pancreatitis is occlusion of the pancreatic ducts; the stoppage may be brought about by gall stones lodged in the papilla of Vater, or as they stress, by metaplasia of the epithelium of the branches of the pancreatic duct. The latter condition was found to exist in 18.6 per cent of autopsies in individuals over 25 years of age. They believe, in contrast to Dragstedt and his co-workers, that because of the obstruction, trypsin and steapsin are liberated and result in necrosis of the

arteries, producing hemorrhage, necrosis of other elements in the pancreatic tissue, and in fat necroses.

The clinical manifestations resulting from chronic or acute pancreatitis are of three varieties, each caused by the involvement of a specific element in the pancreatic tissue. One or the other of these impairments may be present singly or they may co-exist. These symptom complexes will be discussed under the heads:

1. Carbohydrate metabolism
2. Fat metabolism
3. Blockage of the pancreatic ducts.

Carbohydrate Metabolism and the Pancreas

Chronic pancreatitis, due to arteriosclerotic and senescent lesions in the islands of Langerhans, is accepted as being the cause of the mild, slowly progressive diabetes of older persons. This form of diabetes was called essential diabetes by Naunyn and is still known by that name.

In younger individuals, diabetes pursues a much more irregular course, punctuated by periods of marked loss in carbohydrate tolerance. Wilder (quoted by Warfield), and Warfield have suggested that repeated attacks of mild acute pancreatitis, followed by some permanent injury to the islands of Langerhans, might be the reason for this type of diabetes. Case 1 (table 1) is an example of this sort:

Case Report

Case 1. S. R., student, male, in September 1933, at age 18, developed a glycosuria; he had been 14 lbs. overweight; complete physical examination, except for glycosuria and hyperglycemia, was negative in all respects.

The details of the course of the diabetes are shown in table 1.

In any case of acute pancreatitis the degree to which the carbohydrate metabolism is implicated will depend upon the number of the islands of Langerhans that are involved so that an acute pancreatitis may or may not be accompanied by hyperglycemia and glycosuria; an acute pancreatitis may result in diabetes (Case 6), it may bring about no change in the severity of an existing diabetes (Case 5), it may aggravate a diabetes permanently (Case 1), or it may cause the transient appearance of diabetes which subsequently clears up (Case 4).

The oxidation of fat is in part associated with the carbohydrate metabolism. It is an old and accepted principle in the metabolism of diabetes, formulated by Magnus Levy, that: "The fats burn in the fire of the carbohydrates." This does not mean that the oxidation of fats depends entirely on the utilization of glucose but only that the oxidation of B-oxybutyric acid is contingent upon the carbohydrate metabolism. The change from the fatty acids of a chain of 16 or 18 carbon atoms, that go to make up

TABLE I

Date	Urine Glucose %		Insulin * Units per Day		Changes in Glucose Tolerance
	p.m.	a.m.	Individual Dose	Total	
1933 Oct. 16..	0.0	0.0	10–10	20	*Acute onset of diabetes five weeks before.*
1934 May 8...	0.0	0.0	12–8	20	*No change in glucose tolerance during six months.*
July 24..	2.1	2.0	12–10	22	*Exacerbation of diabetes,* abscessed tooth and "swollen jaw" early in July.
Aug. 21..	0.0	0.0	16–8–12–8	44	
Oct. 30..	0.0	0.0	18–10–10–10	48	*Gradual diminution of glucose tolerance for 14 months.*
1935 May 23..	0.0	0.0	20–10–10–14	54	
Aug. 29..	0.0	0.0	24–10–12–14	60	
Nov. 13..	0.0	0.0	26–10–12–16	64	
1936 Jan. 20..	0.0	0.0	26–10–12–16	64	*No change in glucose tolerance for 14 months.*
Sept. 9...	0.0	0.0	26–12–12–16	66	
Dec. 3...	0.0	0.0	*20*–10–*20*–10	60	
Dec. 29..	0.0	0.0	*50*, 10	60	
1937 Jan. 19..	1.5	2.0	*35–35*	70	*Exacerbation of diabetes, with partial recovery of sugar tolerance.* The only cause to which this and the two subsequent exacerbations can be attributed is the nervous strain of taking examinations and entering upon the career of accountant by an ambitious young man.
Feb. 23..	0.0	0.0	*40*, 15–*40*, 15	110	
Apr. 13..	0.0	0.0	*40–30*	70	
Apr. 24..	0.0	0.0	*80*	80	
May 22..	2.5	2.4	*80*	80	*Exacerbation of diabetes.*
June 30..	0.0	0.0	*50–50*	100	
July 29..	1.2	1.3	*50–50*	100	*Exacerbation of diabetes.*

Table 1. Case 1. Four year history of the changes in the loss of sugar tolerance in a diabetic aged 18 years, at the onset of the diabetes. While there have been no signs or symptoms of pancreatitis other than glycosuria, it is suggested that comparatively mild, recurring attacks of pancreatitis are responsible for the irregular progress of the disease.

* Plain figures show regular insulin, italicized figures protamine, or protamine zinc insulin; the individual doses of insulin are separated by a dash.

neutral fats, to the 4 carbon chain of B-oxybutyric acid is governed by other agencies. An excess of B-oxybutyric acid results in diabetic acidosis and coma. A markedly impaired carbohydrate metabolism, therefore, will be associated with acidosis and coma, but the oxidation of fats to the stage of B-oxybutyric acid does not depend upon the islands of Langerhans and their influence upon glucose oxidation. Another part of the pancreas controls the transport and utilization of fat up to the point of B-oxybutyric acid formation. The significance and symptomatology of this pancreatic function will be discussed in the next section on fat metabolism.

Fat Metabolism and the Pancreas

Previous mention has been made of the fact that the complete oxidation of fatty acids and the prevention of acidosis depends upon the proper utilization of glucose. A closer study of cases of diabetes reveals the fact that the disposition of fat is a pancreatic function entirely apart from that of carbohydrate utilization or that of absorption of fats from the intestinal tract. The signs and symptoms of deficient fat metabolism noted in diabetes are:

Hypercholesterinemia
Lipemia
Xanthoma
Fatty liver and spleen.

Hypercholesterinemia occurs in some mild diabetics whose carbohydrate metabolism is well controlled and in whom there is no acidosis. The cholesterol content of the blood parallels the total fatty acids fairly well and may be taken as an index of the degree of lipemia.

Case 2. Male, aged 38: diabetes for four years; observed for more than one year. During that period no insulin was required; nine determinations of blood sugar taken after breakfast were normal, varying from 98 to 167; the blood specimens were always lipemic and the plasma cholesterol was distinctly elevated, ranging from 248 to 400. At no time was there acetone or diacetic acid in the urine. The physical examination was normal except for a large spleen which was tender and whose lower pole extended three fingers' breadth below the costal margin; the liver edge was at the costal margin.

This case was interpreted as being one of diabetes with very marked dissociation of the effects upon the carbohydrate and the fat metabolism. The distinct disturbance of the fat metabolism was evident from the persistent lipemia, the high plasma cholesterol and presumably fat deposits in the spleen, while the carbohydrate metabolism was scarcely affected, since there was only transient glycosuria, the blood sugar was nearly always at a normal level, insulin was not required and dietary restriction alone served to control the situation. The relationship between the elevated blood cholesterol and the control of blood and urine sugar in this instance, is not at all like that which is usually accepted, in that the successful management of the carbohydrate metabolism did not serve to reduce the high level of the blood cholesterol.

Another similar example of dissociated fat and carbohydrate metabolism is Case 3.

Case 3. Male, aged 57: diabetes discovered three years ago on routine urine examination; five years ago accepted on life insurance examination for a large sum. Forty pounds overweight for height and age; otherwise physical examination shows nothing of note. The interesting point in this patient lies in the fact that the plasma cholesterol was continuously high and had a tendency to rise in the face of fairly good control of the diabetes. From August 1935 to August 1937, plasma cholesterol determinations made at intervals, were as follows: 238, 200, 238, 261, 296, 312, 343. 312, 369, 278.

Lough and Killian report the case of a young male diabetic, aged 20, who after seven months' dietary indiscretion, developed xanthoma diabeticorum, lipemia and acidosis. The total fatty acids in the blood were 9,200 (normal 600) and the plasma cholesterol 1,072 (normal 180). In this patient, as in most similar instances, the xanthoma, the lipemia, the glycosuria and the acidosis all cleared up on treatment of the disturbed carbohydrate metabolism; however, here as in many other cases, there was a lag of the return to normal of the lipemia as compared to the blood sugar and the acidosis. This bears out the conception that both the carbohydrate and fat metabolism are affected by an involvement of the pancreas, yet they are not acted upon synchronously and, consequently, it is fair to assume that such changes are brought about by the suppression of a different pancreatic function.

The symptom complex of severe acute pancreatitis,—glycosuria, acidosis, rise of blood cholesterol, lipemia, xanthoma, fatty liver and spleen—often develops so precipitously as to produce a completely baffling picture that defies analysis; on the other hand, there are cases of pancreatitis recorded in which each of these symptoms appears individually and apparently independently of the others. Instances of acidosis without lipemia are common (Herbert); cases of pancreatitis with lipemia or xanthoma developing in advance of, or in the complete absence of glycosuria, are reported. These facts have led Wijnhausen (1921), Joel (1924), Brunner (1935), and Root (1936) to stress the idea that there is a specialized function of the pancreas, which checks lipemia, xanthoma, fatty liver and spleen, apart from the regulation of the carbohydrate metabolism effected by the islands of Langerhans.

A recent case of recurring pancreatitis, with an almost record level blood cholesterol and lipemia, is the following.

Case 4. Male, aged 35, first seen on April 24, 1936.

History: Acute appendicitis, not operated on, 1921 (in view of subsequent events this may have been an attack of acute pancreatitis). March 1935, passed a life insurance examination; September 1935, glycosuria discovered for the first time; December 1935, acute pain in the epigastrium which disappeared in a few days; April 24, 1936, a recurrence of the acute pain in the epigastrium which became so severe that operation was resorted to.

Physical Examination: Markedly obese (85 lbs. overweight for height and age); xanthomata were scattered over the neck, abdomen and legs. The edge of the liver was four fingers' breadth below the costal margin and the liver was distinctly tender; the spleen was not enlarged. The heart rate was 120; there was no other sign of collapse or shock, the patient walking about without embarrassment, and the blood pressure was 132 systolic and 94 diastolic. Otherwise a complete physical examination showed nothing of note.

Laboratory Observations: April 24, twenty-four hours prior to the admission of the patient to the hospital, the urine sugar was 3.3 per cent and acetonuria was graded two plus. The plasma was markedly lipemic. The blood sugar was 400 mg. per cent, the total plasma cholesterol 2037 mg. per cent, and the total fatty acids in the plasma 1738 mg. per cent. Leukocytes numbered 16,800 with 76 per cent polymorphonuclear neutrophiles. April 25, on admission to the New York Post-Graduate

Hospital, the urine still showed marked glycosuria and acetonuria. The blood sugar had decreased to 214 mg. per cent. The leukocytes now were 25,450 with 80 per cent polymorphonuclear neutrophiles. The administration of 140 units of insulin in divided doses over a period of nine hours rendered the urine sugar and acetone free. Within 48 hours after the initiation of intensive treatment and immediately prior to the operative interference, the blood sugar had decreased to 180 mg. per cent, total cholesterol to 1041 mg. per cent, and the fatty acids to 394 mg. per cent.

TABLE II

	Urine			Blood Sugar mg. %	Plasma Chol. mg. %	Protamine Insulin Units	Orange Juice c.c.
	Volume c.c.	Sugar %	Sugar gm.				
4/29/36							
3:30 a.m.	300	2.0	6.0				
6:15 a.m.	520	1.7	8.3				
8:00 a.m.				200	735	100	120
11:00 a.m.				227	655		100
11:30 a.m.	490	1.7	6.8				
2:00 p.m.				211	628		100
5:00 p.m.				179	707		100
5:30 p.m.	500	1.8	9.0				
8:00 p.m.				185	651		100
10:00 p.m.				185	600		100
12:00 p.m.	400	1.0	4.0				100
Total	2210		34.1				Total carbohydrate 72 gm
4/30/36							
8:00 a.m.				164	571	100	100
9:30 a.m.	450	0	0				200
11:00 a.m.				204	598		200
2:00 p.m.				172	535		200
5:30 p.m.	300	0	0				200
8:00 p.m.				149	577		200
10:00 p.m.				206	543		200
Total	750						Total carbohydrate 130 gm.

Table 2. Case 4. The findings on the second and third days post-operative in a case of acute pancreatitis, showing the effect of single large doses of protamine insulin on the urine sugar, blood sugar and plasma cholesterol. The pre-operative cholesterol figures were much higher: 2037 and 1041 mg. per cent.

Operative Findings: On April 27, Dr. R. Franklin Carter operated at the New York Post-Graduate Hospital and his operative notes were: On opening the abdomen the gall-bladder was found to be distended but not acutely inflamed. The abdomen was filled with a yellowish-green pus. When the incision was extended the appendix was found to be hanging over the brim of the pelvis and adherent at the base but not acutely inflamed. The upper abdomen was searched. Adhesions were found between the hepatic flexure and the colon and the lateral abdominal wall. The adhesions were found to be fibrotic and in the adhesions there was found to be a yellow slough behind the colon involving the fat of the colon wall. The duodenum was normal. Looking up above the duodenum along the common duct, pus was found to be exuding through

an opening in the retroperitoneal covering of the common duct and draining into the abdominal cavity. Bile in the gall-bladder was found to be very thick, tar-like in character. *Operation:* cholecystostomy—draining of the abdomen. *Diagnosis:* acute destructive pancreatitis involving chiefly head of the pancreas with biliary obstruction. (No fat necrosis in abdomen.) . General peritonitis.

Post-Operative Course: complete recovery; discharged 27 days post-operative.

Fifty to 75 units of regular insulin daily in divided doses did not control the post-operative glycosuria. Protamine insulin in single doses of 100 units, buffered by moderate amounts of orange juice every few hours, proved to be more satisfactory (table 2).

The lag of the plasma cholesterol as compared to the immediate response of the blood sugar and the glycosuria, as in the case of Lough and Killian and others, is very evident (table 2). This observation is borne out by experiments on human subjects in which a single dose of insulin did not produce any significant change in the blood cholesterol even though the blood sugar changed from a distinct hyperglycemia to hypoglycemia (Bruger and Mosenthal). The distinction between fat and carbohydrate control by the pancreas is thus stressed.

The subsequent history of this case showed that there was complete recovery from the damage to the pancreas; insulin was never required; an anti-obesity diet was followed for two months with a loss of 35 lbs., but at the end of that period he again " ate everything " including starches, and after eleven months had regained all the lost weight. The interesting points here are that the carbohydrate metabolism remained normal though there was some evidence of disturbance in the fat metabolism; the urine remained sugar free, the blood sugar, taken after breakfast, was 93 mg. and 111 mg. per 100 c.c., and no insulin has been used; the plasma cholesterol values on the other hand were somewhat elevated being 256 and 343 mg. per 100 c.c. Uncomplicated obesity, as shown by Bruger and Poindexter, is characterized by a normal level of plasma cholesterol; the high figures here would consequently point to an involvement of the fat regulating structures of the pancreas, whereas the islands of Langerhans controlling sugar utilization had made a complete functional recovery. The independence of the influences of the pancreas upon the fats and the carbohydrates is again emphasized.

The tenderness of the liver in this case and the tenderness of the spleen in Case 2 are noteworthy. It may be that deposition of large quantities of fat in the liver and spleen may result in tenderness and this may prove to be a sign of diagnostic value.

The solution of the problem of the existence of a disturbance in fat metabolism through the pancreas, apart from that regulating the carbohydrate metabolism, may be provided by the discovery of the hormone " lipocaic " by Dragstedt, Van Prohaska and Harms. In their own words this material is described as follows: " a specific substance has been obtained in alcoholic extracts of beef pancreas, that on oral administration to depancreatized dogs treated with insulin, permits survival and prevents and relieves the fatty degeneration and infiltration of the liver of these animals. This substance, for which the name ' lipocaic ' is suggested, is believed to be a new

hormone that is concerned in some way with the normal transport and utilization of fat."

The "lipocaic" awaits clinical trial. It is sincerely hoped that it will prove successful in controlling the lipemia and hypercholesterinemia, so common in diabetes, and the more severe, though less frequent, disturbances —the fatty liver and spleen, and xanthomata. If the thesis proposed here and by others, that there is an independent control of fat and carbohydrate metabolism by the pancreas, is correct, then it would be expected that "lipocaic" should set aside the derangement of the fat metabolism in diabetes, and it might be particularly valuable in preventing the dreaded vascular complications of the disease.

Blockage of the Pancreatic Ducts

The pathognomonic sign of occlusion of the pancreatic ducts is the occurrence of "pancreatic stools"; the typical pancreatic stools are soft, very voluminous in shape, size and consistency, when passed into a bed pan they resemble those of cattle; they are yellowish and glistening (due to the presence of free fat); they are malodorous (due to putrefaction, since the proteins are hemmed in by free fat which permits the growth of anaerobic organisms, but prevents the digestion and absorption of meat, etc.); there are usually from three to six of such bulky movements a day; the laboratory tests of these excreta are not as reliable as the macroscopic appearance just mentioned; free fat and undigested meat fibers should be seen on microscopic examination. There should be an absence of pancreatic ferment, the lack of which can be more reliably demonstrated by examination of the duodenal contents.

The signs of diabetes may precede the appearance of the pancreatic stools (Case 5), or may appear after the closure of the pancreatic ducts has become manifest (Case 6). There are many instances in which occlusion of the pancreatic ducts is not accompanied by diabetes as might be expected according to MacCallum's findings, previously mentioned, that uncomplicated blockage of the pancreatic ducts results in atrophy and sclerosis of the acinar tissue, while the islands of Langerhans are preserved. Whether an existing diabetes remains unchanged or undergoes an exacerbation with stoppage of the pancreatic intestinal secretion depends upon the presence or absence of pancreatitis and the involvement of the pancreatic ducts in diabetics. (Case 6 is abstracted from a previous publication, Mosenthal, 1912.)

Case 5. Male, first seen 12 years ago (1925) when he was 55 years old. There was then a mild diabetes which was readily controlled by diet. Progress was uneventful until October 1928 when there was some vague discomfort in the epigastrium. Two series of roentgen-ray films revealed no definite lesion. During April and May 1929, there was a series of chills and fever about once a week; the chills were severe and were followed by rises in temperature up to 104 and even 105 degrees. At this time typical "pancreatic stools" appeared. During the eight following years the

number and size of the stools could be checked only by the feeding of raw pancreas. The diabetes was not aggravated by the fever and has remained unchanged during the eight ensuing years.

*Case 6.** Male, aged 20. During the latter part of November 1909, he had an attack of intense abdominal pain without diarrhea or fever; one month later a marked glycosuria was found; in January 1910 he had frequent attacks of vomiting accompanied by a "burning sensation" but no frank abdominal pain; in February the vomiting ceased; the stools, however, at this time changed in character, became large and putty-like and were said to resemble "mayonnaise"; the stools have continued unchanged up to the present (May 1910). The results of pancreatic medication are given in table 3.

TABLE III

Urine in Twenty-Four Hours

Date, 1910	Glucose gm.	Total N gm.	Ammonia gm.	Ammonia N as Per Cent of Total N	Total Acid Substances as B-oxybutyric Acid gm.	Number of Stools per Day	Medication
May 11..	137.5	17.5	2.8	13.3	5.3	3	"Pankreon" 0.5 gm. three times a day, May 11–19.
May 12..	88.0	—	0.3	—	—	1	
May 13..	94.7	20.7	1.9	7.7	4.9	4	
May 16..	95.2	—	1.6	—	—	2	Raw sheep's pancreas 50 gm. three times a day, May 20–29.
May 19..	94.0	27.7	2.9	8.3	—	4	
May 24..	45.5	11.8	0.9	6.0	—	1	
May 26..	91.3	26.5	5.2	16.3	29.3	1	
May 27..	68.5	22.4	6.0	22.0	34.8	1	
May 28..	86.5	—	5.3	—	—	0	
May 30..	80.0	—	5.0	—	—	1	

Table 3. Quantitative urinary determinations, and medication in Case 6, pancreatic steatorrhea.

Note: Lack of effect of pancreatic extract, and the good result (reduction of number of stools) with raw pancreas; the raw pancreas brought about a better absorption of fats as shown by the rise of ammonia and acid substances in the urine.

The relief from pancreatic stools can be accomplished only by the administration of raw pancreas. The use of any of the commercial extracts has proved to be valueless (see the effect of "Pankreon," table 3). Case 5 has been taking raw pancreas with satisfactory control of his bowels for eight years; every time he omits the pancreas, the steatorrhea returns. Bargen, Bollman and Kepler recently reported the successful control of pancreatic stools by an extract of pancreatic juice administered in capsules; this should prove to be a great boon because raw pancreas has an exceedingly disagreeable, and to many persons, a very revolting taste.

It is interesting to note that the administration of raw pancreas in Case 6 (table 3) improved the absorption of fat a great deal as evidenced by the increase in the acidosis; today with the availability of insulin this ceases to become a clinical threat, but it is worth bearing in mind that uncontrolled steatorrhea may be a factor in producing malnutrition through non-absorp-

* Case 6 is abstracted from a previous publication (Mosenthal, 1912).

tion of fat; table 3 shows that the absorption of glucose or protein was little, if at all, affected by the administration of raw pancreas.

Summary

Clinical and pathological studies of diabetes point to the pancreas as the crucial organ responsible for the disturbed carbohydrate metabolism that constitutes diabetes. Chronic pancreatitis resulting from senescent processes is responsible for the very slowly progressive essential diabetes of Naunyn. Acute pancreatitis in its milder form, which is much more common than is generally supposed, probably is the cause for the stormy course, with many acute exacerbations, found in younger diabetics; pancreatitis will result in three sets of symptoms which may develop independently or be combined with one another; these are: (1) interference with the carbohydrate metabolism bringing about hyperglycemia, glycosuria, acidosis and coma; (2) disturbance of the fat metabolism manifesting itself in a rise of the blood cholesterol, lipemia, xanthoma, fatty liver and fatty spleen; (3) occlusion of the pancreatic ducts and consequent lack of external secretion of the pancreas into the intestine, causing the characteristic stools and preventing the absorption of fat.

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THE VARIABILITY OF BASAL METABOLISM: SOME OBSERVATIONS CONCERNING ITS APPLICATION IN CONDITIONS OF HEALTH AND DISEASE *

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MEANS, discussing the value of the basal metabolic rate, says: "It should be remembered that basal metabolic rates are never too low (except when a technical error or an inward leak in the apparatus occurs or when the subject goes to sleep). All the factors which tend to make a reading inaccurate tend to make it too high: food, failure to eat properly, emotion, fever and so forth. Therefore a single low reading has more significance than a single high one." Similar statements can be found in the writings of nearly all students of metabolism, including Benedict, DuBois, Krogh, Boothby and others.

That an important truth of immediate practical interest for the standardization and clinical interpretation of determinations of metabolism is conveyed in such statements is not to be denied, and that adventitious departures from the usual "basal" conditions more frequently raise than lower the measured metabolism is true. The term "basal metabolism" for that metabolism measured under defined conditions for standard and clinical purposes usefully emphasized this fact, especially in the early phases of the development of the subject. But as Krogh has stated, it might have been better to have used the term "standard metabolism," for the entire concept has been confused by the implications of the term "basal" and the ideas it embodies. From the truth that basal metabolism is generally lower than metabolism measured under "non-basal" conditions has grown the fallacious idea that basal metabolism is the *lowest* metabolism. From the truth that basal metabolism is less variable than metabolism measured under uncontrolled conditions has insidiously grown an attitude toward basal metabolism as a quantity that is *fixed*. These erroneous ideas are never given explicit statement, but they are tacit implications in a considerable amount of work, even important work by the best authorities.

We wish in this essay to emphasize that "basal metabolism," as an actual observation is one made under certain defined standard conditions, conditions which while well considered and soundly established, are nevertheless to a considerable degree arbitrary; even if these conditions are rigidly adhered to, the measurement will be *variable*, even as is any biologic observation. It

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follows at once that there is no one *lowest* metabolism that has a prerogative to be considered *the* basal metabolism over any other measurement of metabolism made under standard conditions. Were this always realized explicitly, to mention only one consequence there would not be in serious investigations a casual identification of measurements of basal metabolism which are "the lowest observation," "the mean," "the first observation," and so forth for if basal metabolism is a variable, these are not equivalent. It is not to the point at the moment to question whether the distinction between these various representations of basal metabolism is of importance; the fact is that for purposes of certain investigations they are negligible and for others they are essential, but they cannot be *assumed* to be the same.

Once the aspect of variability of metabolism is clearly grasped and deliberately accepted, problems will present themselves, the solution of which will be immediately enlightening, and other old problems will be seen in a different view. It is for these reasons that we have embarked on a careful analysis of a large body of our data, both normal and pathologic, with due regard for the variable characteristics of the material as well as for its central character. Some of these results can be given here.

For the statistical analysis of variability we will make use of the Gaussian curve, the "curve of chance," and the measure of variability appropriate to it as expressed in the "standard deviation." While the correct technical use of statistical methods requires an intensive knowledge of the subject, only a few simple facts need to be known for an investigator unacquainted with the complexities of the subject to understand the significance of those results of our studies which we wish to present here. Therefore, before proceeding to the presentation of some of our findings, we shall review briefly some statistical essentials which will guide what follows.

The Gaussian or "normal" curve is a symmetrical curve, "cocked hat" in shape, and is completely defined mathematically for any given group by two constants, namely, the "mean" and the "standard deviation." The *mean* locates the center of the curve and is the usual *average*. It is calculated as usual by adding all the observations and by dividing the sum by the number of observations. The *standard deviation* (σ, sigma) measures the "spread" or variability of the curve, and it is the value obtained by squaring the difference of each observation from the mean, adding these squares, dividing the sum by the number of observations less one, and finally taking the square root of the result. In other words, $\sigma = \sqrt{\frac{\Sigma\Delta^2}{N-1}}$, where σ is the usual expression for the standard deviation, $\Sigma\Delta^2$ is the sum of the squares of the differences of the individual observations from their mean and N is the number of observations.

The application of the Gaussian curve of chance to problems dealing with biologic data such as we are concerned with arises from the fact that this curve has been found to describe the distribution of biologic observa-

tions, as well as the fluctuations of chance, in a wide variety of situations. It is therefore often referred to as the "normal" curve of distribution. Not all biologic data, of course, can be represented by the Gaussian curve, but if they cannot, that fact is also of significance. If the distribution of the data which are being studied follows the Gaussian curve, then the standard deviation will not only accurately measure the variability of those data in an easily expressed value, but it can also be used directly to give the proportion of cases falling within or outside of any stated limits.

The simplicity of the use of this function is shown in figure 1, where the upper curve represents in the unshaded portion the area within $\pm 0.6745\,\sigma$ or 1 probable error of the mean, and contains 50 per cent of the observations, and each shaded area in the outer horns of the curve represents 25 per cent of the observations. The middle curve represents in the unshaded portion the area within $\pm 1\sigma$ of the mean, and contains 69.3 per cent of the observations (it can be remembered as roughly $\frac{2}{3}$ of the observations), and each shaded portion outside represents approximately 15 per cent of the observations. The lower curve is the most important because, here, the unshaded center represents the area within $\pm 2\sigma$ of the mean, which is the commonly accepted critical limit. It contains slightly more than 95 per cent of the observations, and each outer horn contains only approximately 2.5 per cent of the observations. It is for the reason that the area within $\pm 2\sigma$ of the mean contains almost all (95 per cent) of the observations that 2σ is usually the limit of "significance." That is, if a value is found to be more than 2σ away from the center of a defined group, it is considered as probably not belonging to that group ("significantly different"), and this probability increases rapidly as the limit of 2σ is exceeded, as can be seen from the shape of the curve.

Bearing this in mind, one can see why the standard deviation should be calculated and the observations compared to the normal curve where possible. Instead of being indefinite about the number of cases that lie beyond any given distance from the mean, we can always refer to the value of $\pm 2\sigma$ and this will represent 95 per cent of the total.

A study of the variability of basal metabolism in normal subjects has just been completed by two of us (Berkson and Boothby), and some of the results may be summarized here: First, the variability of repeated determinations for the same person is to be considered, the intraindividual variability. For successive determinations within the same day the average sigma is 1 calorie per square meter per hour (3.0 per cent of the mean); for successive observations made on successive days, under the usual basal postabsorptive conditions, the average sigma for men and women is 1.5 calories per square meter per hour (4.1 per cent of the mean), and the distribution is Gaussian. The intraindividual variability is somewhat greater for women (1.61 cal. per sq. meter per hour, 4.7 per cent) than men (1.33 cal. per sq. meter per hr., 3.5 per cent), and this is attributable prob-

ably to the disturbing effect of the menstrual cycle on the metabolism. It is not to be understood that the intraindividual variability is the same for all ages or for different persons of the same age. In reviewing the published

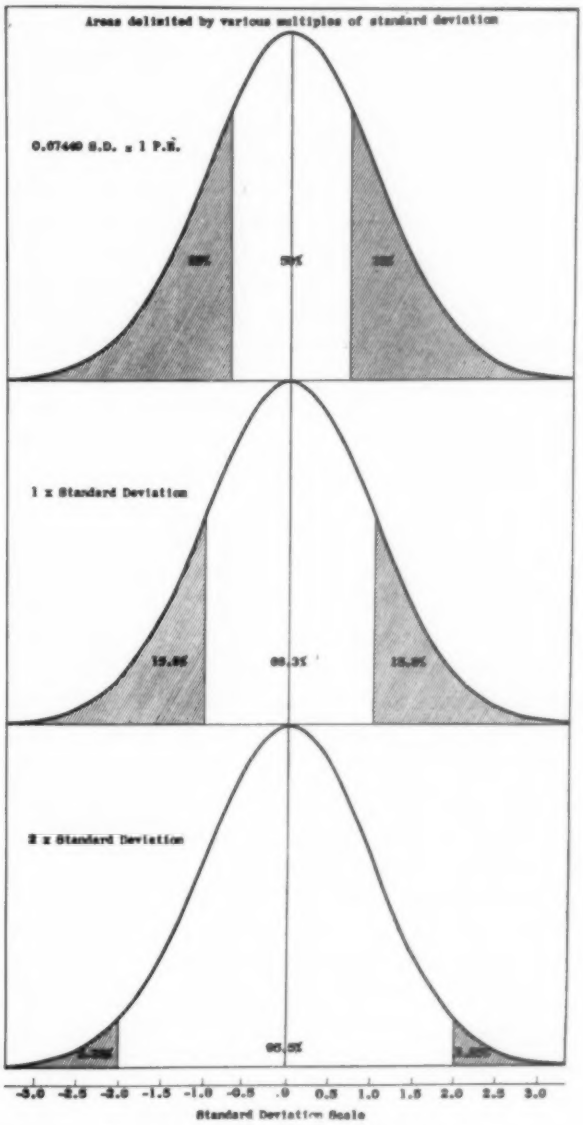
Areas delimited by various multiples of standard deviation
0.67449 S.D. = 1 P.E.
50%
1 x Standard Deviation
68.3%
2 x Standard Deviation
95.5%
-3.0 -2.5 -2.0 -1.5 -1.0 -0.5 .0 0.5 1.0 1.5 2.0 2.5 3.0
Standard Deviation Scale

FIG. 1. Normal or Gaussian curve.

data for the study referred to, we found that Prof. F. G. Benedict had the record for maintaining constancy of metabolism over a long period, the value of his standard deviation being 0.7 calories per square meter per hour (2.2 per cent of the mean).

The variability as between different individuals of the same age, sex, weight, and stature—the interindividual variability—is greater than the intraindividual variability, for it consists of the variation that obtains for the single individual plus that which represents the differences between one individual and another. The sum of these is what we measure in calculating the variability of numerous observations of basal metabolism, each for a different individual (but all of the same sex, age, stature and weight). We found as the interindividual standard deviation for males under 20 years of age, 3.14 calories per square meter per hour (6.5 per cent of mean), and for those 20 years and over, 2.58 (6.7 per cent of mean). For females the standard deviation in the group under 20 years of age was 2.98 calories per square meter per hour (6.8 per cent of mean), and for those 20 years and over, 2.42 (6.9 per cent of mean). These estimates of interindividual variability calculated from single observations made on different individuals is composed, as we have said, of two parts, and we therefore refer to it as the *total* interindividual variability. One part is the variability inherent in repeated determinations for the same person, the intraindividual variability. The other part represents the variability from one person to another, the variability of the "characteristic" or the mean metabolism of different persons.

How much individuals differ from one another apart from their own inherent variability is of considerable biologic interest. However, it is manifestly impracticable to collect a large number of individuals of the same sex, age, stature and weight, and to make for each one a large number of observations to obtain the mean metabolism in order then to calculate directly the variability of those means. Fortunately the value can be estimated indirectly from the calculations already made. Since the total interindividual variability is the sum of the intraindividual variabilities and the variability of means which we are seeking, the variability of mean metabolism can be obtained by subtracting the intraindividual variability from the total. The subtraction is not to be performed by using the standard deviations themselves but rather their squares, because two independent variabilities add their effects as the square-root of the sum of the squares. The square-root of the difference of the squares of the total interindividual variability and the intraindividual variability then, gives the interindividual variability of means. Thus calculated we found for men the value 2.2 calories per square meter per hour (5.8 per cent of the mean), for women 1.81 calories per square meter per hour (5.2 per cent of the mean). Here we found in calories per square meter the variability of men greater than for women, whereas when we considered merely the variability of numerous individual observations we found the female variability larger. We have here, then, the conclusion that if the characteristic (mean) metabolism of the individuals of the species is considered, adult males are more variable than females. Repeated determinations for individual females are, how-

ever, more variable than for males, perhaps as a result of the disturbing influence of the cyclic ovarian function. Therefore, when single determinations for many individuals are used to measure the variability, the total gives a larger net variability for females. It is as though we tried to compare the variability of stature in males and females under circumstances in which the measurement of height in the female was relatively unstable because of posture.

We may now turn to some consideration of observations other than those for normal persons. During the last two decades determinations of the basal metabolic rate as a clinical test have been made in many laboratories and upon thousands of individuals, and it is well established that it is a valuable test for disturbances of the thyroid gland because of its marked increase in hyperthyroid disease and its very low level in hypothyroidism or myxedema. It has at the same time become gradually recognized that the basal metabolic rate is of comparatively little value in the diagnosis of other conditions, in spite of the fact that, in a few, the basal metabolic rate may be definitely affected. The diseases other than those directly associated with the thyroid gland which are known to affect the basal metabolic rate directly or indirectly are the leukemias, the anemias, disorders of the pituitary and of the suprarenal glands, and a few other rare conditions. In addition, on account of respiratory distress, many cardiac patients may have elevated basal metabolic rates; on the other hand, extreme inanition lowers the basal metabolic rate.

During the 10-year period between 1917 and 1926 a large number of patients without thyroid disease were sent to the metabolism laboratory of The Mayo Clinic for the determination of their metabolism. For most of these patients the final clinical diagnosis was some condition which, from everything we know, did not characteristically affect the basal metabolic rate. After excluding, on the basis of a careful and detailed clinical examination, those patients having one of the diseases mentioned in the preceding paragraph which are known to affect the basal metabolic rate, we had for statistical study 7,117 females and 2,397 males, which group for brevity we have designated as the "non-metabolic disease group." In figure 2 is shown the distribution of the observations of the females in this group, and it is seen that the mean of this group is higher, but only by a small amount, 0.7 calories per square meter per hour (1.9 per cent of the standard mean), than a comparable group of normal individuals as judged by comparing them with The Mayo Foundation normal standard. The standard deviation of the distribution is somewhat larger than for a similar normal group, being 3.5 calories per square meter per hour (or 9.7 per cent of the standard mean) instead of 2.5 calories per square meter per hour (or 7 per cent of the standard mean) found for The Mayo Foundation standard. The distribution of the observations for these patients is seen to correspond to the Gaussian curve, as does that for strictly normal individuals. Observations

for the group of males are so similar that it is unnecessary to take space to reproduce the data graphically; the mean for the males is 0.6 calories per square meter per hour above a similar standard normal group (1.7 per cent of the standard mean), and the standard deviation is 3.8 calories per square meter per hour (10.4 per cent of the standard mean).

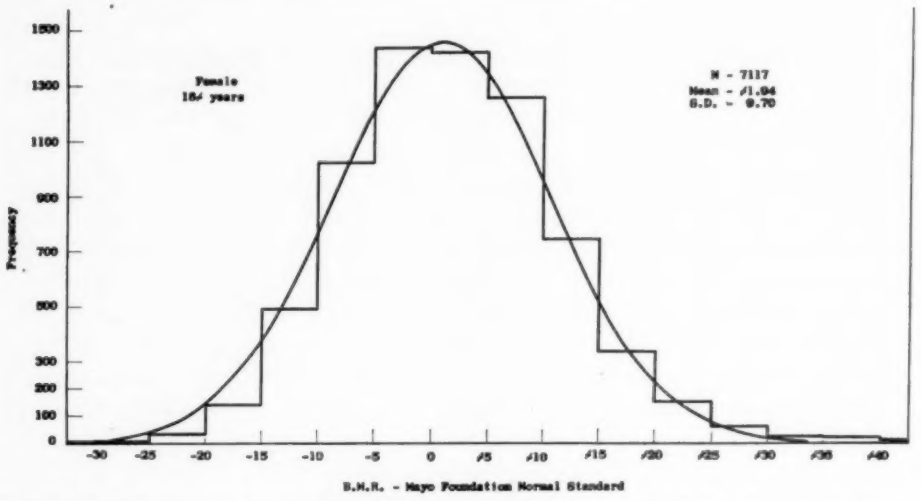

FIG. 2. Distribution of basal metabolism for a group of non-metabolic diseases during a period of 10 years.

The conclusion drawn from this phase of the study is that the largest group of sick individuals sent for a metabolism test, over half of them suffering from so-called chronic nervous exhaustion or neurasthenia, have a basal metabolic rate on the average very slightly higher (2 per cent), and that they have a greater variability (10 per cent), than strictly normal individuals (7 per cent). Using these round figures and remembering that for distributions following the Gaussian curve 95 per cent of the observations fall within ± 2 sigmas of the mean, we conclude that for such a group of patients, 95 per cent of the observations fall within — 18 per cent and + 22 per cent (2 per cent $\pm 2 \times 10$ per cent) on the usual B.M.R. scale measured from The Mayo Foundation Standard.

Let us now give some attention to the pathologic conditions which we usually associate with disturbances of metabolism—typical disease of the thyroid gland. We consider them in three groups: (1) exophthalmic goiter, (2) adenomatous goiter, with and without clinical hyperthyroidism, and (3) spontaneous myxedema. Figure 3 gives the percentage frequency distribution for these disease groups on a single scale for comparison. The observations are shown in histogram form for the three diseases; comparison is made with a distribution for normal subjects which is represented by a smooth curve obtained from the data on which was based The Mayo Founda-

tion standard. In contradistinction to the situation for the normal and non-metabolic disease group, the distributions of the basal metabolism in these thyroid disease groups are not symmetrical Gaussian curves but are

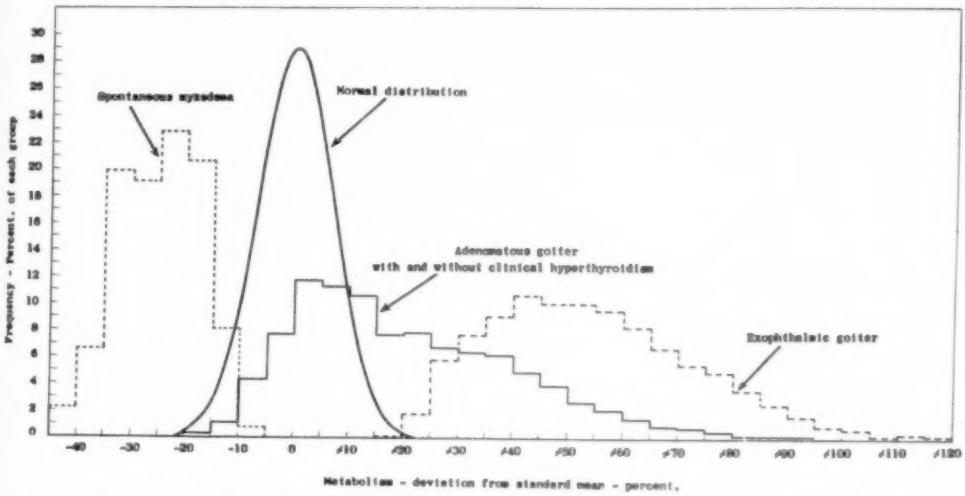

FIG. 3. Basal metabolism in three thyroid diseases compared with group of normal individuals. Percentage frequency distribution for each group.

"skew" (asymmetrical), the hyperthyroid group being skew in the positive and the hypothyroid in the negative direction. That this skewness will have to be taken into consideration to determine the diagnostic significance to be attached to any given B.M.R. determination which departs from the normal standard enough to be considered as possibly pathologic is manifest.

For the exact calculation of the relative probability indicated by such a finding we will have to have a precise delineation of the frequency curves for the abnormals as well as the normals, a task we have not yet completed. Moreover, for the calculation of the probability which a particular metabolism determination denotes, to be used as a criterion for decision in differential diagnosis, other elements enter besides the relative frequencies of the basal metabolism. First among these perhaps are the relative frequencies of the diseases themselves. During the 1917–1926 period referred to, in which there were seen 7,117 females constituting the non-metabolic disease group, there were 3,385 females with exophthalmic goiter, 3,693 with adenomatous goiter, and only 136 with myxedema. The relative probability of any specific disease indicated by a given finding of metabolism will be in proportion to the actual numbers with this metabolism in this disease. In figure 4 is shown the distribution of the actual frequencies for the various disease groups and for different values of metabolism as they were encountered in the metabolism laboratory during this period. The total areas under each curve represent the total actual frequency of the individuals in

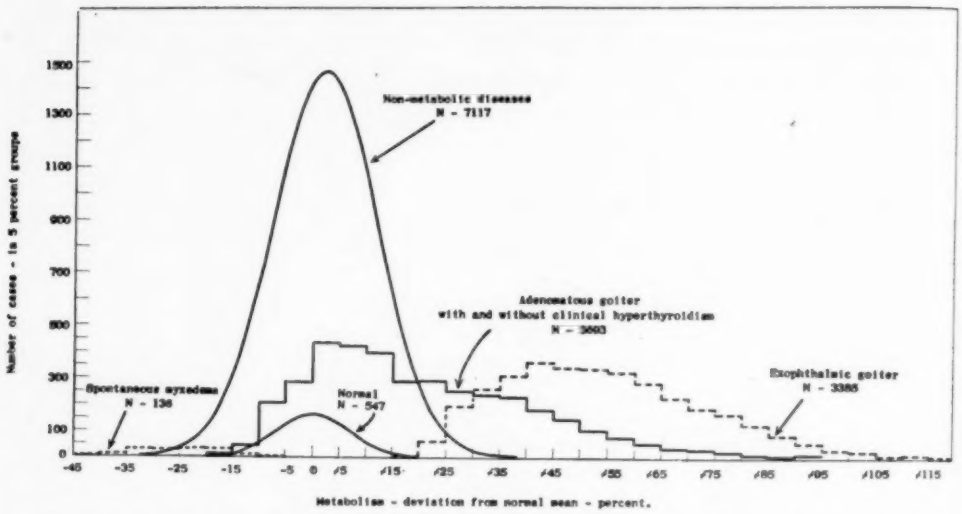

FIG. 4. Comparison of normal distribution of basal metabolism with that for three groups of thyroid disease and a non-metabolic disease group. The frequencies are the number of cases corresponding to each group seen during a 10 year period. The total area under each curve is therefore proportional to the number of individuals in the corresponding group sent to the metabolism laboratory during this period.

the corresponding disease group, and the areas under the portion of the curves corresponding to any values of the metabolism give the relative frequencies and therefore probabilities of the diseases indicated by those values of metabolism.

This brief outline is not intended to be a complete analysis of the various questions touched on, but rather to present some ideas which a consideration of the variability of metabolism suggests. While even the precise study of the variability of metabolism of normal and different disease groups and its correlative probabilities will not in themselves make possible a precise differential diagnosis among metabolic and non-metabolic disease —indeed it will only corroborate the impression that clinical observation must play a large rôle here—such studies are not without importance for the diagnostic problems of the clinician.

It may be noted, though we do not wish to elaborate on the point at this time, that the entire curve for adenomatous goiter (with and without clinical hyperthyroidism) is well to the right of both that for the normal individuals and for the group with "non-metabolic diseases."

In conclusion we wish to emphasize that it is important to study the distribution of cases in each disease group on the percentage basis (that is, on the assumption that one is as likely to encounter a patient with one disease as the other) in order to compare the characteristic basal metabolic findings in each disease. In addition it is equally important to take into consideration the relative frequency with which patients having different diseases present

themselves in a given clinic for study and differential diagnosis if one is to evaluate the probability of a given B.M.R. indicating one or the other condition. This latter point is illustrated in figure 4, in which the graph is based on the actual number of cases occurring in each group in a given period and it is obvious that most of the patients sent to the metabolism laboratory of The Mayo Clinic, who have a B.M.R. between — 15 and — 20 per cent *do not have mild myxedema,* but rather are normal individuals so far as their metabolic rate is concerned; if, however, as in figure 3, the comparison is made on the assumption, which of course is contrary to the fact, that the number of cases of myxedema is equal to those in the other groups, then it appears as though it were nearly an even chance that an individual with a B.M.R between — 15 and — 20 per cent might have myxedema. On the other hand, if the proportion of patients in different disease groups is not very dissimilar, essentially similar deductions will be made whether the frequency is plotted on a percentage basis or on the actual number of cases. For example, the graphs in both figure 3 and figure 4 show that there are many patients with adenomatous goiter who have a B.M.R. between + 15 and + 20 per cent, while only relatively few patients who have exophthalmic goiter have a B.M.R. between + 15 and + 20 per cent.

Finally it must be recognized that " basal metabolism " as an actual observation, under any defined standard condition, is variable, like any biologic observation, and in consequence no one *lowest* metabolism has a prerogative to be considered *the* basal metabolism over any other measurement made under the defined conditions.

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

CARDIAC HYPERTROPHY: ITS RELATION TO CORONARY ARTERIOSCLEROSIS AND CONGESTIVE HEART FAILURE*

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THE cause of hypertrophy of the heart has aroused the interest of pathologists and clinicians for more than three centuries. The hypertrophy of skeletal muscle after increased effort led to the belief that, similarly, cardiac muscle hypertrophied because of increased work. Hypertrophy of the left ventricle in patients with hypertension or aortic insufficiency, and hypertrophy of the right ventricle in pulmonary stenosis or tricuspid valvular disease lent plausibility to this theory.

Certain phenomena, however, associated with hypertrophy of the cardiac musculature have not been readily explicable on the basis of the above hypothesis of increased cardiac work. In animals in which experimental valvular lesions were produced such as aortic insufficiency, increased work of the heart undoubtedly led to hypertrophy, but the degree of hypertrophy occurring even in the most successful experimental instances was much less than that observed clinically in similar lesions.[11] That cardiac hypertrophy is not due solely to increased work is also suggested by the lack of relationship between the degree of valvular obstruction and the degree of hypertrophy seen in man. These considerations have led observers in the past to consider the possible influence of other factors in the production of hypertrophy.

It appeared from analysis of the literature that the significance of nutritional effects had not been fully established. It seemed to us that more information bearing on this phase of the problem might be obtained by ascertaining in a consecutive series of patients whether those hearts which showed advanced arteriosclerosis differed in weight from those showing little or no such change. No case was included in the series that showed evidences of hypertension, syphilis, rheumatic heart disease, anemia, or other factors which would give rise to increased work on the part of the heart. Patients who had congestive failure associated with advanced coronary sclerosis were considered in a separate group in order to study the importance of congestive failure itself in the production of hypertrophy.

The purpose of this communication is to present the results of this study

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and to appraise the significance of two factors in the causation of cardiac hypertrophy: (1) a diminished coronary circulation; (2) the influence of chronic congestive heart failure.

Methods and Results

To evaluate the rôle of coronary artery disease in producing hypertrophy of the heart, the cardiac weights of an unselected consecutive series of patients that had come to postmortem examination were studied. To learn the significance of a diminished coronary circulation uncomplicated by other factors, all cases with any antemortem evidence of congestive failure and all cases showing signs or symptoms of conditions acknowledged to be of possible significance in the production of cardiac hypertrophy such as hypertension, valvular heart disease, mediastino-pericarditis, long continued anemia, leukemia, or thyrotoxicosis were eliminated. Hearts showing slight degrees of aortic stenosis of arteriosclerotic origin were also excluded. To rule out the existence at any previous time of arterial hypertension is always difficult since the fluctuations in blood pressure in this condition always render it theoretically possible that the blood pressure may have been elevated prior to the first recorded physical examination or between the various examinations listed. In order to minimize this possible error, the past history was carefully investigated in each case and the blood pressure measurements obtained on previous admissions in other hospitals, by outside physicians and by life insurance examinations were considered. The upper limit of normal blood pressure was taken as 160 mm. mercury systolic and 90 mm. mercury diastolic. The blood pressure data obtained during a final illness were considered with reservations. Cases in which death was associated with shock due to acute coronary occlusion, intestinal obstruction, perforation of a viscus, or hemorrhage were, of course, excluded unless evidence of a normal blood pressure prior to the final illness was available.

The heart weights of a consecutive group with advanced coronary disease were then compared with a similarly consecutive group showing little or no coronary disease, all cases with the above mentioned factors that might produce cardiac hypertrophy having been eliminated. The only error inherent in this separation of the two groups would be that of possibly overlooking involvement of a portion of some coronary branch; this error would lead to the false inclusion of some cases in the group with little atherosclerosis and so make any differences between the two groups less striking.

In classifying the degree of atherosclerotic involvement of the coronary vessels, the following criteria were employed: grade I, all large branches free from atheromatous changes; grade II, scattered atheromata but no ulcerations or striking changes in the surface of the intima; grade III, the intima covered with atheromatous plaques and inclusion in the pathological report of a definite statement by the examining pathologist to the effect that

there was no narrowing of the lumen at any point; grade IV, as in grade III with one or two sites of slight narrowing; grade V, as in grade IV but with greater degree of narrowing; grade VI, complete obliteration of one major coronary branch such as the left anterior descending, left circumflex or right coronary with little or no narrowing of other branches; and grade VII, complete obliteration of one branch but with marked changes and narrowing in another or all coronary branches.

Figure 1 shows the distribution of cardiac weights in 31 consecutive subjects with advanced coronary disease (grades IV–VII) as compared with 38 cases showing little coronary disease (grades I and II). The ages in the group with marked coronary arteriosclerosis varied from 49 to 80 years and averaged 62 years; in the patients with little arteriosclerosis the ages varied from 50 to 76 years and averaged 61 years; nine of the former

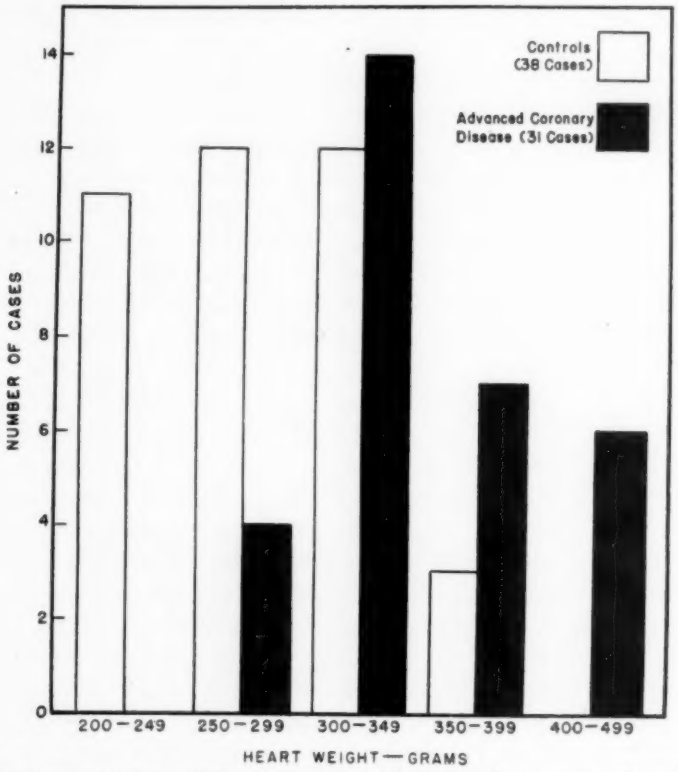

FIG. 1. Comparison of heart weights in patients with advanced coronary sclerosis with those showing little or no coronary sclerosis.

group and 14 of the latter group were females. (Table 1.) Of the 31 hearts showing advanced coronary arteriosclerosis, eight were classified as grade VII; six, grade VI; fifteen, grade V; and two, grade IV. Nine of the 31 cases died of coronary thrombosis. Of the 38 hearts showing but little coronary arteriosclerosis, 26 were classified as grade I, 12 as grade II.

TABLE I

Data in Series of Patients with Little or No Coronary Arteriosclerotic Heart Disease

No.	Age	Sex	Ht. Wt. Gm.	Degree Coronary Disease	Blood Pressure at Final Illness		Cause of Death
					Systolic	Diastolic	
1	65	F	200	1	110	60	Pneumonia
2	76	M	200	2	116	72	Carcinoma of stomach
3	58	M	200	2	142	62	Carcinoma of stomach
4	72	M	210	1	100	55	Pneumonia
5	55	F	210	1	90	60	Hodgkin's disease
6	64	M	215	1	110	64	Carcinoma of colon
7	53	F	220	1	120	85	Carcinoma of colon
8	51	F	220	1	140	90	Pneumonia
9	55	F	220	1	120	65	Pneumonia
10	72	M	240	2	135	90	Carcinoma of lung
11	68	F	240	2	140	60	Pneumonia
12	68	F	250	1	145	85	Carcinoma of cecum
13	63	M	250	2	150	90	Pneumonia
14	63	M	250	1	88	60	Carcinomatosis
15	58	M	260	1	120	70	Carcinoma of colon
16	62	F	260	2	90	54	Septicemia
17	56	F	260	1	128	78	Peritonitis
18	73	F	270	2	110	70	Pneumonia
19	60	M	270	2	128	60	Pneumonia
20	52	M	280	2	150	60	Malignancy of spine
21	73	M	280	1	125	70	Liver abscess
22	55	M	280	1	114	70	Carcinoma of stomach
23	51	F	280	1	90	55	Peritonitis
24	65	M	300	2	110	74	Post-operative shock
25	50	M	300	1	95	65	Carcinoma of esophagus
26	64	M	300	2	122	88	Carcinoma of colon
27	55	M	300	1			Pneumonia
28	51	F	310	1	110	82	Peritonitis
29	57	M	320	1	120	80	Carcinoma of lung
30	59	M	320	1	130	75	Pneumonia
31	62	F	320	2	140	90	Pneumonia
32	65	M	320	1	120	60	Pneumonia
33	76	M	320	1	150	90	Carcinoma of liver
34	51	M	340	1	130	80	Peritonitis
35	60	M	340	1	140	80	Pneumonia
36	62	M	350	1	124	70	Hemorrhage of gastric ulcer
37	59	M	360	1	120	80	Carcinoma of esophagus
38	51	F	380	1	130	90	Pneumonia
	Average Weight 275				M 24		Grade 1 = 26
	Age 61				F 14		2 = 12

The range of distribution of cardiac weights of the cases with advanced coronary arteriosclerosis was definitely higher and the average weight was 348 grams. The mean heart weight of the cases with little coronary atherosclerosis was 275 grams. Although the group with marked coronary arteriosclerosis showed a higher weight distribution, there were few very heavy hearts; the heaviest weighed 440 grams and only six weighed more than 400 grams. Blood pressures taken a few months to two years prior to the final illness were obtained in cases 30, 28, and 20 to 26 inclusive. The pressures varied from 110 to 142 mm. systolic and from 60 to 80 mm. diastolic. The blood pressures in the remaining three cases with heart

weights above 350 gm. were obtained soon after admission to the hospital before the terminal stages of the illness; in two of these latter three instances the history recorded that previous examinations showed no evidence of an elevated blood pressure.

TABLE II

Data in Series of Patients with Advanced Arteriosclerotic Heart Disease

No.	Age	Sex	Ht. Wt. Gm.	Degree of Coronary Disease	Blood Pressure at Final Illness		Cause of Death
					Systolic	Diastolic	
1	63	M	260	5	140	88	Peritonitis
2	69	M	280	5	134	72	Carcinoma
3	59	M	290	5	110	60	Carcinoma of stomach
4	58	M	290	6			Coronary thrombosis
5	77	M	300	6	142	64	Coronary thrombosis
6	73	M	300	5	150	85	Carcinoma of sigmoid
7	63	F	300	6	118	64	Amputation and sepsis
8	52	M	310	7	150	90	Pericolic abscess
9	60	M	314	7	140	70	Pneumonia
10	53	F	320	5	124	80	Meningitis
11	80	F	330	7	160	90	Pneumonia
12	50	M	330	5	150	60	Brain tumor
13	57	M	340	5	140	80	Lymphatic leukemia
14	54	F	340	5	100	40	Coronary thrombosis
15	72	M	340	5	150	70	Carcinoma of colon
16	66	M	340	5	130	80	Central nervous system disease
17	75	F	340	6	130	80	Coronary thrombosis
18	49	F	340	7	80	40	Coronary thrombosis
19	59	M	350	4	132	110	Pneumonia
20	68	M	360	7	140	70	Pneumonia
21	58	M	360	5	120	80	Coronary thrombosis
22	62	M	380	7			Hemorrhage of gastric ulcer
23	54	M	380	6	130	100	Coronary thrombosis
24	62	M	380	5			Coronary thrombosis
25	63	F	380	7	100	75	Coronary thrombosis
26	73	F	400	6			Pneumonia
27	72	M	410	4	140	75	Carcinoma of stomach
28	49	M	420	7	146	78	Carcinoma of lungs
29	75	M	420	5	135	80	Pneumonia
30	64	F	440	5	135	60	Cirrhosis of liver
31	56	M	440	5	140	85	Brain tumor

To determine the influence of congestive failure in the production of cardiac hypertrophy, a consecutive series of necropsy reports of patients in whom congestive heart failure had occurred before death were examined. Cases in which hypertension, valvular disease, mediastino-pericarditis, or any of the other accepted causes of cardiac hypertrophy had been present were excluded. A series of 17 cases remained for study, 15 of which showed advanced coronary arteriosclerosis, falling in groups V to VII above (table 3). The cardiac weights of this series were compared with the previously mentioned series of cases showing advanced coronary atherosclerosis but no congestive failure (figure 2). The higher incidence of

greater heart weights in cases with congestive failure is striking (figure 2). With but one exception, the cases with congestive failure showed cardiac weights of 400 grams or over, 11 being 500 grams or over. Of the latter 11, five were 600 grams or over. These findings are in contrast with those in the group with advanced coronary atherosclerosis but no congestive failure

TABLE III

Congestive Failure

No.	Sex	Age	Ht. Wt. Gm.	Degree of Coronary Disease	Duration of Congestive Failure
1	F	70	330	6	Few weeks
2	M	60	400	7	Few weeks
3	M	75	400	7	Few months
4	M	65	450	6	2¼ years
5	M	65	450	5	2½ years
6	M	55	490	7	One month
7	M	59	500	5	1–6 years?
8	M	63	500	7	1½ years
9	M	63	520	5	One year
10	M	58	520	5	2 years
11	M	67	540	7	4 years
12	M	68	580	7	2 years
13	M	58	600	2	2 years
14	M	64	720	7	3–4 months
15	M	59	730	7	13 years
16	M	57	735	7	4 years
17	M	77	740	3	1½ years

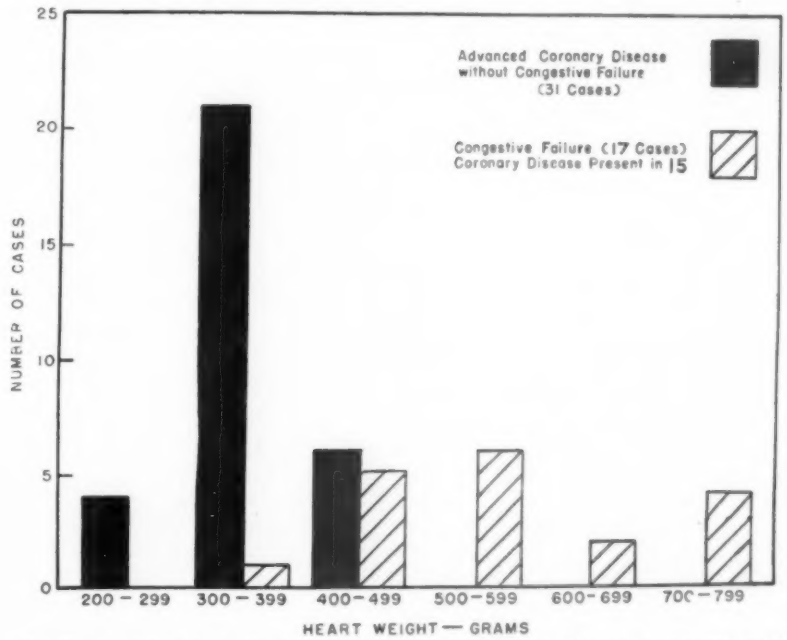

FIG. 2. Cardiac weights in patients with advanced coronary disease compared with heart weights in patients with congestive failure.

in which no cardiac weight above 440 grams was observed. In addition to the data presented above, the progressive increase in heart size could be followed by frequent roentgenograms in two patients with recurrent attacks of congestive failure due to coronary atherosclerosis who eventually came to postmortem examination.

Case Reports

Case 1. (L. S.) This male, aged 63, had had angina pectoris for seven and a half years, and during the past year was admitted to the hospital three times for congestive failure. On his first admission on December 10, 1935, he complained of palpitation, dyspnea on exertion, cough and nocturnal dyspnea of two months' duration. Physical examination showed cardiac enlargement, gallop rhythm, râles at both bases, an enlarged tender liver, and edema of the legs and over the sacrum. A seven foot roentgenogram taken in the out-patient clinic on June 4, 1929, showed a transverse cardiac diameter of 14.7 cm. (table 4). A second roentgenogram taken on November

Table IV

Cardiac Enlargement in the Course of Congestive Heart Failure

L. S	6/4/29	11/13/34	11/27/35	2/2/37
	cm.	cm.	cm.	cm.
R.	5.9	4.6	7.2	7.1
L.	8.8	9.1	11.3	12.5
T.	14.7	13.7	18.5	19.6
Ch.	29.5	30.0	28.2	29.6
G. V.	7.0	6.8	8.0	7.9
L.	13.9	15.5	17.5	
B.	10.5	11.3	11.7	
H. B.	3/17/30	11/2/32	3/13/33	3/23/33
	cm.	cm.	cm.	cm.
R.	6.2	9.5	9.4	10.2
L.	12.1	12.6	12.4	12.6
T.	18.3	22.1	21.8	22.8
Ch.	28.5	29.4	28.0	30.2
G.V.	7.5	11.2	8.0	8.4
L.	17.5	20.0	21.1	21.0
B.	13.8	17.1	15.8	17.8

13, 1934, showed a transverse diameter of 13.7 cm. Thus, there had been no change in the cardiac measurements during a period of five years. Just prior to this admission to the hospital, however, the roentgenogram showed a transverse cardiac diameter of 18.5 cm., an appreciable increase presumably in part due to acute dilatation accompanying the congestive failure. Seven days after this admission he was discharged improved, but a few months later, March 30, 1936, he was readmitted for congestive failure and remained in the hospital for 14 days. Eight months later, January 14, 1937, he was admitted a third time for congestive failure. At the end of the first week he was free of edema and allowed to be up and about the wards. A seven foot roentgenogram was then taken on February 2, 1937, and this showed a transverse diameter of 19.6 cm. The increase in cardiac size during the past year was greater than apparent from the roentgenographic measurements, for the increased transverse diameter of 18.5 cm. the year before was associated with congestive failure presumably associated with some acute dilatation. He died suddenly on February 3, 1937, and postmortem examination revealed no cardiac dilatation. The heart weighed

500 grams. The coronary distribution was studied with injection and roentgenographic methods by Dr. Monroe Schlesinger and found to be the seat of extensive coronary sclerosis and occlusion. A tremendous collateral circulation had developed. The changes in heart size are recorded in table 3 and figure 3. The cardiac size showed a progressive increase during the period of congestive failure.

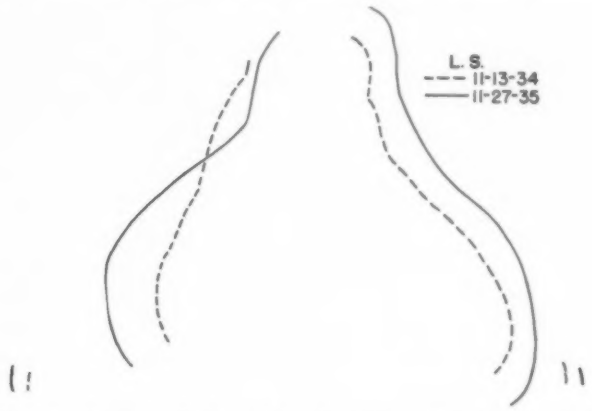

FIG. 3. *Case 1.* Increase in heart size in course of congestive heart failure.

Case 2. (H.B.) This male, aged 57, was admitted to the hospital on March 8, 1930, complaining of dyspnea on slight exertion and edema of the ankles of two weeks' duration. Examination showed cardiac enlargement and auricular fibrillation, and the electrocardiogram showed bundle branch block. In the course of the next three years with the exception of a few months he was not free from congestive failure and was almost completely confined to bed. Transverse diameters of subsequent seven foot roentgenograms showed a progressive increase in heart size (table 3). Necropsy on January 26, 1934, showed evidence of an old mitral lesion with calcification of the mitral ring, thickening and some retraction of the valve cusps. There was, however, no appreciable incompetency of the valves. The slight mitral lesion had undoubtedly been present for many years, and therefore it probably did not have any influence on the cardiac enlargement during his recent illness. The coronary arteries showed an extreme degree of sclerosis with numerous points of occlusion. The heart weight was 735 grams. Figure 4 shows the increase in size in the course of heart failure.

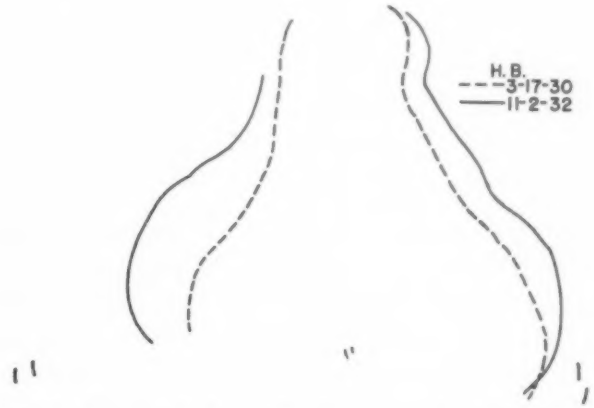

FIG. 4. *Case 2.* Increase in heart size in course of congestive heart failure.

Discussion

The foregoing results do not solve the problem of cardiac hypertrophy but are of value in appraising the etiological importance of two contributory influences, coronary arteriosclerosis and congestive failure, which are frequently operative but often neglected in discussions on the subject. The early studies of Corvisart in 1806,[35] and the emphatic views of Cohnheim [36] in 1882, as well as the supporting opinions of many later investigators, have stressed increased work as the stimulus causing hypertrophy of the cardiac musculature. Clinical experience, as well as many experimental investigations, has thrown doubt, however, upon the validity of the view that cardiac hypertrophy can always be ascribed entirely to increased work. Practically all investigators agree that cardiac hypertrophy is found under conditions demanding increased work of the heart but many observers have stated that various other factors may play a contributory or even a dominant rôle; their views may be conveniently grouped under the following headings:

1. *Elevated Metabolism.* In thyrotoxicosis the heart weight has been found increased by numerous observers. This increase may be due (1) to coincident marked cardiovascular disease or latent heart disease made manifest by the hyperthyroidism, (2) to overwork consequent to the elevated metabolic rate, or (3) to a specific toxic effect on the heart. Only in the latter two instances can the hypertrophy be ascribed to the thyroid disease itself. Failure to evaluate coincident organic disease has vitiated many of the reports on this subject and has led to varied opinions.[13, 27] An analysis of the available data indicates that cardiac hypertrophy occurs only infrequently in uncomplicated thyrotoxicosis and then only to a slight degree.[21, 22] Experimentally, cardiac hypertrophy has been produced by the administration of thyroid, but the conditions of the experiments and the criteria of hypertrophy employed do not permit unquestionable clinical application of the results.[23, 24, 25, 26] In chronic lymphatic leukemia in which there is an elevated metabolic rate unassociated with hyperthyroidism, post mortem examination has revealed the average heart weight increased 75 grams above the normal.[16] It is of interest that in frizzle fowl in which species the metabolism is elevated, the hearts are reported as definitely hypertrophied.[3, 4]

2. *Increased Physical Exertion.* There is a divergence of opinion regarding the effect of exercise on the weight of the heart, some maintaining that the heart weights of athletes fall within the range of normal for individuals of the same size and age who have not engaged in prolonged strenuous exercise, while others believe that prolonged exercise leads to definite hypertrophy. In accord with this latter view Tung and his coworkers [20] state that definite cardiac enlargement of the heart as seen by roentgen-ray was found in 45 per cent of their series of 46 ricksha pullers; no heart weights, however, are given. Steinhaus [29] has discussed this aspect of the problem in detail.

3. *Anemia.* Cardiac hypertrophy at post mortem has been found in pernicious anemia in the absence of other factors to account for it.[5] Similarly, Porter [17] by roentgenographic studies found an increased heart size in the anemia associated with hookworm disease and obtained suggestive evidence of hypertrophy, inasmuch as the heart size, while becoming smaller after alleviation of the anemia, did not return to normal.

4. *Coronary Arteriosclerosis.* Miller and Weiss [15] reported 19 cases with advanced arteriosclerotic involvement of the coronary vessels unassociated, however, with any evidence of cardiac hypertrophy, leading them to the conclusion that advanced coronary artery disease does not necessarily cause gross cardiac hypertrophy. The cardiac weights in two instances were, however, 350 and 400 grams. Similarly, Horine and Weiss [12] found no roentgenological evidence of cardiac enlargement in 20 patients with coronary thrombosis observed by periodic seven foot roentgenograms from five months to nine years after the initial attack. It is not likely that small changes in heart weight would be readily translated into changes in the seven foot roentgenogram. Bartels and Smith,[1] on the other hand, in a study of patients with myocardial infarction found heart weights of 400 grams or more in 26 of 42 patients, the largest heart weighing 715 grams. These authors stated that in none of these 42 cases was there any evidence of any condition commonly supposed to produce hypertrophy. No statement is made, however, regarding the presence or absence of congestive failure. Nemet and Gross [18] in their study of the inter-relationship of arteriosclerotic heart disease and chronic congestive failure report 11 patients of their series of 100 who showed no evidence of congestive failure. Of these 11 cases, seven showed heart weights less than 400 grams; two were above 400 grams and two showed generalized microscopic hypertrophy of muscle fibers. Coronary artery disease sufficiently marked to cause coronary thrombosis was found to be the sole factor in producing cardiac enlargement in only 11 of a series of 128 patients with enlarged hearts reported by Parkinson.[19]

5. *Other Defective Nutritional States.* Cardiac hypertrophy has been observed experimentally after the injection of spartein sulphate and adrenaline chloride.[7] In two cases in the literature in which the left coronary artery arose from the pulmonary conus [2, 6] marked left ventricular hypertrophy was found in the absence of valvular defects; the supply by the left coronary artery of venous blood under the decreased pulmonary arterial pressure was evidently the causal factor. That cardiac enlargement might be due to defective nutrition of the heart muscle because of deficient coronary blood supply consequent to the fall of mean arterial pressure was advanced as a cause of hypertrophy by Lewis and Drury [31] in their study of the pathological physiology of arteriovenous aneurysm. These authors further stated that defective nutrition is probably the cause or contributing cause of cardiac hypertrophy in such conditions as aortic regurgitation, coronary arteriosclerosis, anemia or any condition in which the output of the heart is

decreased or the mean arterial pressure is much reduced. Willius and Smith [32] report hypertrophy of the heart in several children who survived for only short periods following their first rheumatic infections and in whom inflammatory lesions of the heart were widespread. Willius and Smith conclude that the severe myocarditis of these children was the chief factor contributing to the production of cardiac hypertrophy, since the valvular deformity was relatively slight. The coexistence of congestive heart failure in at least three of these four cases makes interpretation of their findings difficult. Myocardial degeneration due to unknown causes has been found in cases of marked idiopathic hypertrophy of the heart.[14]

6. *The "Injury Theory" of Cardiac Hypertrophy.* Among the numerous other theories to account for cardiac hypertrophy, that first enunciated by Horvath,[28] later supported by the pathological studies of Albrecht [33] and more recently strengthened by the important experimental observations of Eyster [8, 9, 10] seems most satisfactory, since it provides a common denominator according to which practically all forms of hypertrophy become understandable. Horvath [28] strenuously objected to the work theory of hypertrophy and asserted that the fundamental cause of hypertrophy of any muscle from whatever stimulus lay in stretching of muscle fibers greater than normal. This stretching acts as a common causal factor of both work and of hypertrophy, the latter two being results and in no way interrelated as cause and effect. He stated that the uterus hypertrophies without work during pregnancy and that the eye muscles and diaphragm accomplish much work but are not under tension and do not hypertrophy. Albrecht [33] described histologic evidences of muscle injury preceding hypertrophy, and stated that interference with the normal nutrition of the heart preceded hypertrophy. The experimental observations of Eyster and his associates [8, 9, 10] are of considerable importance. These investigators produced aortic regurgitation in dogs, following which roentgenograms showed definite acute dilatation of the heart, reaching its maximum on the third to sixth day and disappearing by the tenth day. Subsequently, hypertrophy gradually developed. Similar dilatation and subsequent hypertrophy were induced by creating aortic stenosis by constriction of the ascending aorta with a rubber band. In one group of animals the band was removed after from three to six days when dilatation had reached its maximum and before hypertrophy had occurred. The hearts subsequently hypertrophied to an extent comparable to that occurring in the dogs in which the bands were allowed to remain intact. During the period of initial dilatation the muscle wall was thin and stretched, and hydropic degeneration became evident. After hypertrophy had developed there was an increase in size of the individual fibers without increase in fibrous tissue. The hypertrophy was therefore considered to be a reaction to injury brought about by the sudden dilatation.

The above theory as to the cause of hypertrophy was termed by Eyster [8]

the " theory of injury " and would seem to provide a common denominator for most of the various types of hypertrophy. Thus, any condition which imposes an increased initial tension on cardiac muscle such as hypertension, valvular defects, or congenital defects is in accord with this theory. Hypertrophy in conditions in which prolonged impaired nutrition of the heart muscle exists is likewise readily understandable for the consequent dilatation or stretching again acts as the causal factor. The experimental studies of hypertrophy following inflammation or the injection of toxins, the occurrence of hypertrophy in leukemia and pernicious anemia, the left ventricular hypertrophy in some instances of so-called idiopathic hypertrophy in which the left coronary artery carries venous blood at lower pressures because of its anomalous origin from the pulmonary artery are instances which are in accord with this concept.

Our own observations presented in this communication provide strong clinical support to the " injury theory " of Horvath, Albrecht and Eyster as well as affording insight regarding the degree to which hypertrophy of the heart may be ascribed to coronary arteriosclerosis itself. The fact that the group of patients with moderate or advanced arteriosclerosis were similar in all other respects, such as age, clinical condition, etc., to the group with slight or no coronary arteriosclerosis permits one to conclude that slight or even moderate cardiac hypertrophy is frequently, though not necessarily, associated with the more advanced degrees of arteriosclerotic involvement of the coronary arteries. The occurrence of cardiac hypertrophy in many conditions in which the work of the heart is increased makes it difficult to ascertain the degree to which other factors are operative in the production of the hypertrophy; in the patients described above, conditions requiring increased work by the heart were not present.

It is reasonable to infer on the basis of the involvement of the coronary vessels and the presence of diffuse focal changes noted in such hearts that the nutrition of the musculature is impaired. Dilatation or stretching of the fibers under such circumstances leads to subsequent hypertrophy; when the degree of impairment is greater, more marked consequences ensue and congestive failure supervenes. As shown by Starling and his associates,[34] such dilatation is in the nature of a beneficial response since it enables the heart for the moment to increase its capacity for work. The fact that all patients with considerable coronary arteriosclerotic involvement do not show hypertrophy is probably due to the development of adequate collateral circulation which compensates in such cases for the localized diminished blood supply.

Our data also indicate that the existence of congestive failure in itself leads to the development of hypertrophy. It has often been inferred that the largest hearts in congestive failure were enlarged initially and fail because of the previous dilatation and hypertrophy. According to this concept, congestive heart failure is the failure of the hypertrophied heart. If this were so, one would expect to find such large hearts before the onset of

failure in at least a few instances in an unselected group of patients with advanced coronary arteriosclerosis. Slightly increased weights were observed by us in this group (table 1) but the degree of hypertrophy was never great.

In brief, our data indicate that with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy; with more severe involvement a slight degree of hypertrophy is encountered presumably due to impaired nutrition of the muscle fibers causing them to undergo stretching and consequent hypertrophy. In patients who have suffered from congestive failure the weights of the hearts are considerably increased. This finding might be interpreted as being the direct result of more advanced degrees of arteriosclerotic involvement of the heart, the concomitant congestive failure playing no significant rôle. Our data, however, suggest that while the advent of congestive failure may be due to severe impairment of nutrition, the more striking degrees of cardiac hypertrophy observed in such patients are largely consequent to the development of congestive failure itself and rarely occur in its absence. In accord with this concept, the degree of cardiac hypertrophy seemed generally proportional to the severity and duration of congestive failure.

Summary and Conclusions

The purpose of this communication is to present the results of the findings in patients with various degrees of coronary arteriosclerosis in order to appraise the significance of two factors in the causation of cardiac hypertrophy: (1) a diminished coronary circulation; (2) the influence of chronic congestive failure.

The cardiac weights of a consecutive series of patients were studied to learn whether those hearts which showed advanced arteriosclerosis differed from those showing little or no such change. No case was included that showed evidences of hypertension, syphilis, rheumatic heart disease, anemia, or other factors which would give rise to increased work on the part of the heart.

The cardiac weights of the cases with advanced arteriosclerosis showed a definitely higher range of distribution than the cases in a comparable series with but little coronary arteriosclerosis. There were, however, few greatly hypertrophied hearts in the cases showing advanced coronary arteriosclerosis; the heaviest weighing 440 grams and only six of the 31 weighing more than 400 grams. In a comparable series of patients in whom congestive failure was also present, 16 out of 17 showed heart weights above 400 grams and eleven above 500 grams.

The data indicate that with the lesser degrees of coronary arteriosclerosis the heart undergoes little or no hypertrophy; with more severe involvement a slight or moderate degree of hypertrophy is encountered presumably due to impaired nutrition of the muscle fibers which causes them to undergo

stretching and consequent hypertrophy. In patients who have suffered from congestive failure, the weights of the hearts are considerably increased.

These results support the "injury theory" of Horvath, Albrecht, and Eyster of the causation of cardiac hypertrophy rather than the widely held "work hypertrophy theory."

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AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT

EFFECT OF VITAMIN C ON THE CULTURE OF H_{37} TUBERCLE BACILLUS *

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MANY infectious diseases have been shown to be accompanied by a subnormal urinary excretion of cevitamic acid—vitamin C. Presumably the cevitamic acid has been altered or destroyed, directly or indirectly, by the action of the infecting organisms. That this may be true is shown by the development of scurvy in spite of ample gastrointestinal intake of cevitamic acid in the food. Marin [1] reports such an instance and thinks the destruction of the vitamin was due to *Bacillus coli* or paratyphoid B in the intestine. His patient failed to recover by oral anti-scorbutic treatment. Steppe [2] showed this destruction of vitamin C experimentally. He found that various types of coli and paratyphoid react differently on vitamin C under the same cultural conditions. The pH apparently had no influence. Some of the organisms destroyed the vitamin in 24 hours. On the other hand, the vitamin has a definite influence on some bacteria and upon bacterial and other toxins. It will not, however, replace the growth promoting substances found in some media (Koser et al.[3]). Von Gagyi [4] studied the effect of various organisms upon vitamin C and the effect of vitamin C upon the same organisms. He worked with coli communis, paracoli, typhoid, paratyphoid, dysentery, saprophytes and the tubercle bacillus. He found that the tubercle bacillus lived at least 70 hours upon media containing five parts cevitamic acid per 1,000. A change in virulence of these tubercle bacilli was not determined up to the time of his publication. Boissevain and Spillane [5] found that growth of H_{37} tubercle bacilli occurred only after the cevitamic acid content had fallen below 0.001 per cent. The synthetic cevitamic acid content of the medium was kept more or less constant by the addition of cevitamic acid every three days. Although when this was done the pH was within the range of growth, no growth took place when the concentration of the vitamin was 0.001 per cent or higher. However, no protective action against H_{37} was produced in guinea pigs by the administration of 50 times the antiscorbutic dose of cevitamic acid. This confirmed the work of others who failed to find such a protective action.

In a series of experiments with cevitamic acid given by vein, Heise, Martin and Schwartz [6] found that the sensitivity to tuberculin was lessened and the blood sedimentation speed reduced in a proportion of tuberculous patients, although Heise and Martin [7] could demonstrate no protective action

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of cevitamic acid against tuberculous infection in guinea pigs, in a preliminary test. Interest was naturally aroused as to the possible effect of cevitamic acid upon the growth of the tubercle bacillus upon a medium of known content.

Experimental Procedure

Twenty c.c. of Proskauer and Beck's synthetic medium were placed in each of four flasks. To two of them 100 mg. of cevitamic acid were added. The $H_{37}Rv$ (Steenken) variant of tubercle bacilli was seeded into the bottom of the medium in each flask. Growth was much more abundant in the

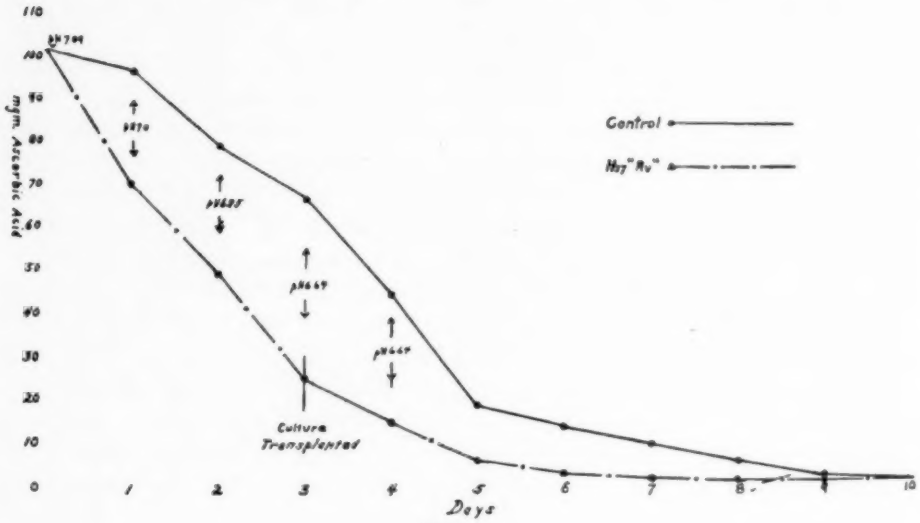

Fig. 1.

control flasks. Daily subcultures were made for the first four days and subsequently every third day for five weeks upon slants of Hohn's medium —pH 6.5. Abundant growth appeared on subcultures of the controls within eight days but the subcultures from the cevitamic acid cultures developed only a few colonies and showed a growth lag three to five times as long as in the controls. After ten days growth developed more rapidly than previously in all cevitamic acid cultures and in the subcultures. All transplants to Hohn's medium were further subcultured on the same medium to determine whether there were differences in growth characteristics. None was noted after 40 days.

Virulence

Four guinea pigs were inoculated intratesticularly with some of the less typical deepseated growth from the cevitamic acid flasks. All of the pigs reacted, intradermally, to 5 per cent O.T. two weeks after inoculation. Death from generalized tuberculosis occurred in all four pigs within 90

days. Growing colonies from two of the Hohn's medium subcultures of the cevitamic acid flasks were inoculated into guinea pigs. The colonies were isolated and raised somewhat in structure. About 30,000 bacilli, dry weight, from each of two colonies that had different structure than the parent colony were inoculated into two pigs. These pigs were controlled with the inoculation of two pigs with a typical parent colony. All four pigs reacted intradermally to 5 per cent O.T. two weeks after inoculation. Death from generalized tuberculosis occurred also in these four pigs within 90 days.

To discover whether the lag period noticed in the previous experiments was due to the reaction of the medium, another experiment was performed. To each of two flasks containing 20 c.c. of synthetic medium, 100 mg. of partially neutralized cevitamic acid were added. The flasks were incubated at 37.5° C. for five days. Small portions of the medium were removed for titration with sodium 2, 6-Dichloro-Benzenone-indo-3-chlorophenol (Eastman) from time to time and it was found that no unchanged cevitamic acid remained after seven days. The color of the medium was then a burgundy. The contents of each flask were then neutralized with N/10 NaOH until the pH corresponded with that of the medium in two control flasks, viz., pH 7.2. H_{37} Rv variant was floated on the surface of the medium in all four of the flasks, two containing reduced cevitamic acid and two controls. Growth was slower in the presence of reduced cevitamic acid than on the controls. Growth characteristics and microscopic morphology were the same in all flasks. Animal inoculations were not made.

The above experiment was repeated but instead of allowing the cevitamic acid to become entirely changed, 100 mg. of the partially neutralized acid were added to the two experimental flasks every third day. (Previous determinations had shown the rate of change in the synthetic medium used; see table.) Such additions were carried out for a period of nine days—a total of 300 mg. At this time a marked difference in the growth characteristics was noted in the two cevitamic acid flasks as compared to the controls. Growth was denser and less spreading in the cevitamic acid flasks. It appeared as small raised islands with but little of the veil-like intervening growth which characterized that in the control flasks. The cevitamic acid medium growth resembled that of an Ra variant rather than an Rv variant. Changes in the reaction of the medium * as noted in the table were too slight to have accounted for the variations in growth.

The experiment of growing the bacilli in the constant presence of cevitamic acid was carried out in another way. The Rv variant was floated on the medium and then subcultured on similar medium every third day. The controls were treated likewise. Two thousand one hundred mg. of cevitamic acid were used. Again the growth resembled that of an Ra rather than an Rv variant as appeared in the controls. On the cevitamic acid

* We are indebted to Dr. Eric Alling for making pH determinations with a glass electrode.

medium the growth appeared as an elevated island without a veil-like periphery, whereas on the controls the growth was flat, veil-like and extended up the sides of the flasks.

Virulence Tests

Four guinea pigs were inoculated intracerebrally, two with approximately 2,500 organisms, dry weight, from the cevitamic acid culture and two with the same dose from the control cultures. All four pigs reacted to 5 per cent O.T. intradermally two weeks after inoculation and died of tuberculosis of the brain within 34 days.

Six other pigs were inoculated subcutaneously with about 5,000 organisms; three from the cevitamic acid cultures and three from the control flasks. No change in virulence was noted at autopsy.

Summary

The addition of cevitamic acid to Proskauer and Beck's synthetic medium alters the character of the growth of tubercle bacilli floated on it. On this medium Rv variants of the H_{37} strain develop like Ra variants whereas in control broth without cevitamic acid the growth retains its Rv characteristics. There is no associated alteration in the virulence of the organisms.

Note: The cevitamic acid used in these experiments was donated by Merck and Company, Rahway, N. J.

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CASE REPORT

CONGENITAL DISPLACEMENT OF THE TRICUSPID VALVE (EBSTEIN'S DISEASE): REVIEW AND REPORT OF A CASE WITH ELECTROCARDIOGRAPHIC ABNORMALITIES AND DETAILED HISTOLOGIC STUDY OF THE CONDUCTION SYSTEM *

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CONGENITAL anomalies of the tricuspid valve unassociated with other major cardiac malformations are rare. However, there may be atresia of the valve, with or without stenosis of the right venous ostium; only one or two leaflets, or as many as four, five or six leaflets; excessive development of the valve with atresia of one leaflet; an extra leaflet fused with one of the normal leaflets; congenital neoplastic hyperplasia of the valve; displacement of the valve downward into the right ventricle; or even transposition of the tricuspid and mitral valves. Herxheimer [1] (1909–1913) reviewed briefly the reported cases of such anomalies, which, of course, have been augmented since his study. In 1866 Ebstein [2] described the first definite case of congenital displacement of the tricuspid valve, and since that time at least 14 essentially similar cases have been recorded, making, with the new case described in this report, a total of 16 certain cases in the literature.

REVIEW OF THE LITERATURE

Ebstein's patient (1866) was a man of 19 years who had had dyspnea and palpitation of the heart since childhood. For two years before death he had had a productive cough. For 16 days before death he had presented symptoms and signs of heart failure with tricuspid regurgitation, as well as manifestations of tuberculous pneumonitis. The heart was greatly enlarged. There was a forceful pulsation and a thrill over the precordium. A long murmur, beginning in systole but running through diastole and obscuring the heart sounds, was heard best at the base of the heart, on the right side, and also in the back. The second pulmonic sound was not accentuated. At necropsy the right auricle was found to be hypertrophied and widely dilated. The Thebesian valve was absent. The foramen ovale was not completely closed and the flap contained several fenestra, one quite large. In the large right ventricle was seen a large membrane springing from part of the annulus fibrosus, the anterior and posterior walls of the ventricle and partly in its posterior and inferior half from the interventricular septum. Its external and under surface was attached to the anterior and lower wall of the ventricle by chordae tendineae and papillary muscles. This repre-

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sented the fused and downwardly displaced anterior and posterior leaflets of the tricuspid valve. The membrane was white and glistening and fenestrated, especially in its lower half. These fenestra opened into a space between the outer surface of the membrane and the wall of the ventricle. About 15 mm. below the annulus fibrosus a small flap arose from the endocardium of the interventricular septum with its base above and its apex below, whose edge was attached by chordae tendineae to the endocardium. This represented the isolated and malformed septal or medial leaflet of the tricuspid valve. It formed, with the anterior portion of the large membrane, an oval opening measuring 4 by 3 cm. into the conus arteriosus. The right ventricle was greatly dilated. The left auricle and ventricle were normal. The malformation of the heart, therefore, consisted mainly of an anomalously formed and downwardly displaced tricuspid valve which divided the right side of the heart into a large auricular portion consisting of the true auricle and the greater part of the ventricle and a smaller ventricular portion consisting of the lower portion of the true ventricular cavity and the pulmonary conus. During ventricular systole part of the blood in the latter ventricular portion undoubtedly ejected blood both into the pulmonary artery and back into the auricular portion. Until the time of the terminal heart failure the excess blood in the auricular portion probably passed through the patent foramen ovale, thus preventing positive venous pulsation and passive congestion of the viscera. Ebstein explained the murmur as being due in its systolic component to blood rushing back into the right auricle and venae cavae and in its diastolic component to the blood streaming into the cavity of the ventricle over the surface of the not entirely smooth membrane. Besides the cardiac findings the necropsy revealed active and advanced pulmonary tuberculosis and congestion of the viscera.

Marxsen [3] described the next case of this cardiac anomaly in 1886. The patient, a woman aged 61 years, developed profuse diarrhea with a high fever and rapid pulse rate after the extraction of a mature cataract. At necropsy the cardiac findings were apparently unexpected, and there was no passive congestion of the viscera. Death had been due to ulcerative colitis. The right side of the heart was very large, the left small. There was thickening of the mitral valve. The tricuspid valve was represented by a pouch-like membrane composed of three indistinctly differentiated and fused components. The membrane was attached to the wall of the ventricle much as in Ebstein's case, but the septal component was not isolated but was fused with the anterior component. The posterior component was attached vertically downward along the interventricular septum, the very large anterior component to the anterior wall of the ventricle. There were numerous small chordae tendineae holding the edges of the valve down to the wall of the ventricle and the moderator band without the intervention of true papillary muscles. The largest component was almost fused to the wall of the ventricle. The valve opened into the pulmonary conus through an aperture 3 cm. in diameter. The foramen ovale was patent, and the Eustachian valve was well developed. The pulmonary conus was broad and hypertrophied.

MacCallum's [4] case (1900) was similar. The patient was a man who had always been blue and who died at the age of 30 years of pulmonary tuberculosis. At the necropsy there was found chronic tuberculosis of the lungs and chronic passive congestion of the viscera. The heart was enlarged, especially the right side. The Eustachian valve was persistent as a large apparently functional

valve. The valvula foraminis ovalis also persisted but was not competent to close the foramen ovale, which was open to a width of about 1 cm. The very large appendix auriculae opened by two mouths into the auricle which was somewhat constricted near its middle by a muscular ring. The tricuspid valves were ballooned out into the right ventricle and had apparently become closely grown together with the ventricular wall. Two of the segments were visible against the interventricular septum and toward the left as wrinkled, folded membranes, which were very soon fused with the ventricular wall and were apparently functionless. The remaining membrane seemed to furnish the whole membrane which lined the ventricular wall and septum and which below, roofing the trabeculae, formed the floor of a sort of intervalvular chamber. The latter opened into the ventricle through a round orifice situated toward the left just below the conus arteriosus and guarded by a flap-like fold of the chamber wall. It further opened through several small fenestra, each guarded by tiny valves which were furnished with chordae tendineae and papillary muscles. The pulmonary artery was slightly narrowed, and the ductus arteriosus persisted as a cord, but otherwise the heart was approximately normal.

Schönenberger's [5] case (1903) was that of a girl four and a half years old who was found to have cyanosis and clubbed fingers. There was an intense thrill over the precordium, and systolic and diastolic murmurs replaced the heart sounds. The area of cardiac dullness was greatly increased to the right, and bronchial breath sounds were heard over the right lung. Death occurred suddenly. At necropsy the heart was found to fill nearly the whole of the right hemithorax, and the right lung was thin, indurated and almost completely calcified. The wall of the right ventricle appeared to be a thin membrane distended with blood. The left ventricle was very small with firm, thick walls, a thickened endocardium and numerous chordae tendineae between the papillary muscles. The pulmonary artery was small compared to the aorta. The auricles were very large. A large membrane resembling a sail hung down in the right ventricle as in Ebstein's case and apparently represented the fused anterior and posterior components of the tricuspid valve. There was an exaggerated moderator band between the conus arteriosus and the remainder of the right ventricle from which arose a papillary muscle with chordae tendineae attached to the large membrane and to the upper part of the conus arteriosus near the pulmonary valve. Other papillary muscles existed lower down in the right ventricle with chordae tendineae attached to the membrane. A smaller independent leaflet was attached to the septum, probably representing as in Ebstein's case the septal leaflet of the tricuspid valve. There was an oval opening into the conus arteriosus between the membrane and the moderator band, and small fenestra also existed in the membrane near its edge where it was attached to the chordae and papillary muscles. The large auricular portion of the right ventricle was very thin-walled and contained almost no muscle tissue. The foramen ovale was wide open. Eustachian and Thebesian valves persisted.

Geipel [6] (1903) reported three cases of Ebstein's disease. The first was that of a museum specimen of a male aged 18 years; the second was also that of a museum specimen; and the third was that of a male aged 15 years who for three months had had edema of the legs and extreme weakness. This patient had some cyanosis; the heart was enlarged to left and right, there was gallop rhythm, and the heart sounds were weak and diffuse. There were pulmonary

râles. Just before death thrombosis occurred in the left femoral vein and the right jugular vein, and an embolus lodged in the Sylvian artery. In all three cases there was great enlargement of the right side of the heart. In the place of the normal tricuspid valve a broad band or a sack hung far down into the right ventricle, as in the cases previously described. The anterior leaflet was the best developed in all three cases, and it fused with the somewhat less well developed posterior leaflet. The septal leaflet was the most poorly developed. The orifice into the conus formed by the free edge of the anterior leaflet, the septal leaflet and the prominent moderator band was triangular or oval. In case 3 it was multilocular due to excessive development of muscular elements in conjunction with the valve. In case 1 papillary muscles were either completely lacking or were very rudimentary. Numerous chordae tendineae were present in all three cases, either in groups or discrete; they were longest on the anterior leaflet, so that that leaflet, the largest, was most free. The septal leaflet was practically devoid of chordae. The foramen ovale was patent or fenestrated in each case, but the left auricle was not enlarged in any. Geipel called attention to a case described by Riecke [7] in 1831 which he considered to be the first recorded case of this anomaly of the tricuspid valve, but while there are certain resemblances it is certainly not the same malformation. In Riecke's case there were major defects of the right auricle; the tricuspid valve was absent, and some muscular trabeculae (but not a valve) divided the right ventricle into two cavities.

Malan's [8] case (1908) was that of a 60 year old man who had presented manifestations of heart trouble for two years before death. The heart was moderately enlarged, and there was a loud systolic murmur. The liver was enlarged, and slight edema was noted. At the necropsy numerous splenic infarcts and thrombosis of the right iliac and the mesenteric artery were found. The left ventricle was hypertrophied and fibrotic. The right auricle and ventricle were enlarged. The tricuspid valve stretched downward toward the apex. The anterior component was large and attached partly to the annulus fibrosus and partly to the anterior wall of the ventricle. The other two leaflets were small and attached to the interventricular septum. The passage between the auricular portion of the right heart and the conus arteriosus was formed by the wall of the ventricle and the anterior leaflet. The valve was attached to the myocardium directly by means of chordae tendineae. A large Eustachian valve was present.

Heigel [9] (1913) also reported three cases of this congenital anomaly. The first case was that of a girl of 10 years who had always been well until a week before death, when she vomited, became apathetic and complained of substernal pain and then became somnolent with a pulse rate of 56 per minute. An early systolic murmur was noted. There was a little cyanosis. Necropsy showed an early cerebral abscess with a localized purulent meningitis. The liver was congested. The right auricle and especially the right ventricle were enlarged, the latter being three times as large as the left ventricle and giving the impression of a thin-walled sac. The foramen ovale was wide open, and the Eustachian and Thebesian valves were well developed. In place of a normal tricuspid valve there was a broad connective tissue septum which was attached to part of the annulus fibrosus and to the anterior wall of the right ventricle down as far as the apex and to the interventricular septum in its lower part. This had a large anterior and a smaller posterior component with an opening between, from the edge of which short chordae tendineae passed to a small papillary muscle in the

conus arteriosus and to the moderator band. A slit-like opening into the conus was formed by the thickened free edge of the anterior component and the upper part of the interventricular septum. The lower free edge of the anterior component was attached by chordae tendineae to another small papillary muscle in the conus. A small remnant of a septal leaflet was attached to the upper part of the interventricular septum, and in the septum below this there was a large thickened plaque in the endocardium. The left auricle was not enlarged. The posterior leaflet of the mitral valve was divided by a cleft into two equal parts. There was some thickening of the free edges of the mitral valve and some of the chordae tendineae. There were two small areas of thickening of the left auricular endocardium.

Heigel's [9] second case was a case previously studied by Verocay in 1907. The patient was a girl, aged 3 years, with cyanosis and clubbed fingers and toes, who died of measles with bronchopneumonia. She had been thought to have pulmonic stenosis. The heart was very similar to that of the first case, but papillary muscles and trabeculae were absent or very rudimentary, and the mitral valve was not abnormal. The foramen ovale was open.

Heigel's [9] third case was that of a museum specimen of 1855 which Treitz had studied. The patient was a woman aged 38 years who died of "paralysis cordis." The right heart was quite similar to those of the two previous cases, but the anomalous tricuspid valve was thicker and roughened and was attached directly to papillary muscles without chordae tendineae. Also, the foramen ovale was closed and the auricular portion of the right ventricle was not so large. The right auricle and left ventricle were dilated, and in the left ventricle below the aortic valve and on the membranous septum there was a large thickened plaque.

Blackhall-Morison and Shaw [10] (1919) reported the case of a man of 38 who had had "heart trouble" for three years and who died of pulmonary and meningeal tuberculosis. There had been marked accentuation of the first heart sound and a precordial systolic bruit. The right auricle and ventricle were both dilated and hypertrophied. The columnae carneae were decidedly hypertrophied and especially one running downward and outward from the base of the posterior cusp of the pulmonic valve. The tricuspid orifice was dilated. The septal leaflet of the tricuspid valve was "fleshy" and "sessile." The anterior leaflet was redundant and attached in its normal position. The posterior leaflet coalesced at its right boundary with the right limit of the anterior cusp but was attached abnormally low in the ventricle, and its left portion was divided into two parts. A large, tough umbrella-like flap was attached to the ventricle close to its apex, and a second smaller portion was "fleshy" and "sessile." The foramen ovale was closed, and there was a well developed Thebesian valve. There was also congenital absence of one kidney with abnormal development of the ureter on the same side.

Blackhall-Morison [11] later (1922) reported the case of a man of 33 years who had been known to have heart trouble since the age of 21 years and who died suddenly. The heart was a typical specimen of Ebstein's disease. The right heart was much dilated and its wall very thin. The auriculoventricular orifice admitted the whole hand. The largest leaflet of the valve was the anterior, and the septal leaflet was small and attached vertically to the septum. There were two large papillary muscles. The membranous portion of the interventricular septum was abnormally large. The foramen ovale was closed.

Arnstein's [12] case (1927) differed from those previously described mainly in that the posterior leaflet of the tricuspid valve was the largest. The anterior leaflet was thick and suggested a trapeze. Both anterior and posterior leaflets were attached largely to the papillary muscles directly. The medial leaflet was attached directly at its free edge to the septum by short, delicate chordae tendineae. All three leaflets were joined together, the medial one not being independent as in some of the other cases described. There were two openings into the conus arteriosus, a smaller medial one and a larger lateral one. In the wall of the auricular portion of the ventricle the myocardium was practically absent. The pulmonary valves were thin but somewhat grown together, with slight stenosis. The foramen ovale was open, and the Eustachian and Thebesian valves were well developed. The patient was a woman of 20 who had had cyanosis of the lips, nose, ears and fingers since early childhood, with palpitation and dyspnea on exertion and latterly pressing pain over the sternum. Clubbing of the fingers had existed since the age of 14 years, and the patient had never menstruated. She developed symptoms and physical signs of advanced pulmonary tuberculosis, which caused death. The heart was moderately enlarged, and there was a systolic-diastolic thrill over its left side. Over the middle of the sternum a long diastolic murmur was heard, while at the apex and the tricuspid area there was a loud, long systolic murmur and a short diastolic murmur. The cervical veins were distended but not pulsating; the liver was neither enlarged nor pulsating. Toward the end edema appeared, but the cyanosis became less intense.

Finally, the case of Bassen described briefly by Abbott [13] (1928) was that of a lad of 16 who died of erysipelas. He had had palpitation of the heart and dyspnea for several years and for two years precordial pain, some edema of the legs, and cyanosis of the lips and nailbeds. There was a very wide area of cardiac impulse with great enlargement of the heart to the left, and there were systolic and diastolic thrills at the apex, and systolic murmurs were heard over the entire precordium. At necropsy chronic passive congestion of the viscera and congenital absence of the left kidney and ureter were found. The heart was greatly enlarged, due mainly to a much dilated right auricle, and the right cardiac chambers had extremely thin walls. The tricuspid valve was absent from its usual site, but near the apex of the right ventricle there was a membranous leaflet with a stenosed multilocular orifice leading into a small ventricular cavity communicating directly with the pulmonary artery. This membrane was attached to numerous papillary muscles by "uneven" chordae tendineae. The foramen ovale was widely patent. The left ventricle was slightly dilated and hypertrophied. The mitral valve was slightly thickened along the line of closure. This was undoubtedly a case of Ebstein's disease with definite tricuspid stenosis as well as regurgitation.

Case Report *

Clinical Course. The patient was a white woman, aged 21 years at the time of her death. On October 4, 1930, at the age of 15 years she had first been examined at the Lymanhurst School Heart Clinic of Minneapolis, at which time she had stated that a diagnosis of heart disease had been made when she was 7 years old. There was no history of rheumatic infection. She had no complaints, and her general condition was good. She was a well developed, well nourished school girl. There was no cyanosis or clubbing of the fingers. The heart was enlarged both to the right

* Army Medical Museum Accession No. 50981.

and the left. The heart sounds were slow and regular. A harsh, blowing systolic murmur was heard along the left border of the sternum, with maximum intensity in the third left interspace. This murmur replaced almost the entire heart cycle and suggested a congenital lesion, but there was no thrill. The second pulmonic sound was somewhat accentuated. Roentgenographic examination revealed marked cardiac enlargement, and a lateral film made with the esophagus filled with barium showed definite posterior displacement of the esophagus. The transverse thoracic diameter was 24.0 cm.; and the total transverse diameter of the heart was 15.0 cm., with M. L. measuring 9.2 cm. and M. R., 5.8 cm.

The patient was not seen again until January 11, 1933. She still had no complaints and looked very well. The heart was essentially the same except for the presence of frequent premature contractions. The vital capacity was 1500 c.c.

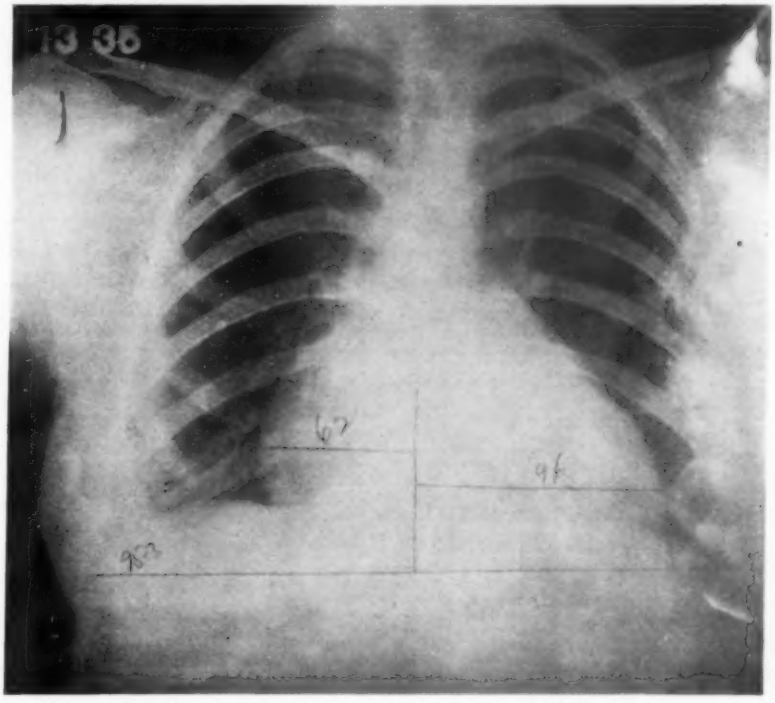

FIG. 1. Enlarged heart, especially toward the right.

Roentgen-ray examination revealed the same marked cardiac enlargement, with the measurements all slightly greater than before.

When examined again on March 31, 1934 she was well except for some dyspnea. The hands were now cold, clammy and cyanotic, and there was a suggestion of clubbing of the fingers. The vital capacity was 1420 c.c.

On March 13, 1935 the findings were essentially the same, but cyanosis and clubbing of the fingers were not definite. There were numerous premature beats. The long, harsh murmur was best heard in the fourth interspace just to the left of the sternum and seemed to occupy the entire heart cycle. It was fairly well transmitted toward the apex but was not heard beyond the precordium nor in the neck. The second pulmonic sound was not audible. The blood pressure was 104 systolic and 90 diastolic. The roentgenogram showed the heart to be considerably enlarged to both sides (figure 1). There was no enlargement in the region of the superior or

median convexities, and although the enlargement in the region of the right auricle was most marked and unusual the contour of the heart could not be said to be typical of any lesion. The transverse thoracic diameter was 25.3 cm.; the total transverse diameter of the heart was 15.8 cm., with M. L. measuring 9.6 cm. and M. R., 6.2 cm. The vital capacity was only 1000 c.c. The electrocardiogram showed left axis deviation; rate 72; PR interval 0.16 sec.; occasional ventricular premature beats; QRS 0.16 sec. in Leads I and II, and 0.12 sec. in Lead III; P-wave positive in all leads; T-waves in Lead I variable and either positive or negative (figure 2). The second lead was most interesting in that it showed changes in the shape of the main ventricular complexes, suggesting that the excitation wave was taking different directions at different times.

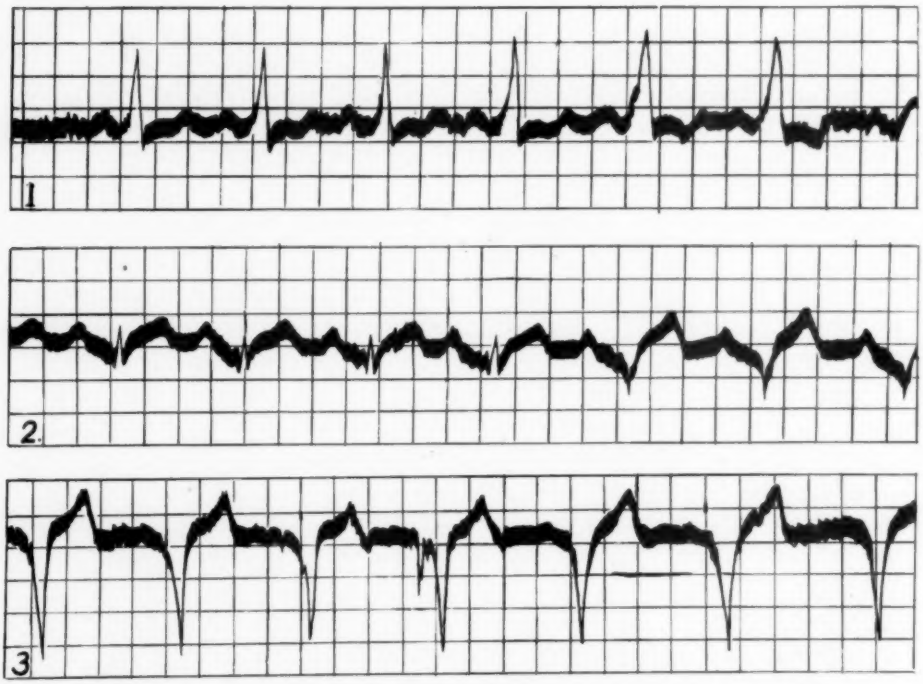

FIG. 2. Conventional three leads: left axis deviation; prolonged QRS complexes; variation in form of ventricular complexes, Lead II.

The patient attended a dance on the night of June 29, 1936 and was apparently in her usual good health when she retired at 10 p.m. Her parents were awakened by a noise in her room at about 2 a.m. the same night and upon investigation found her to be dead in bed.

Necropsy. Necropsy was performed at 9:30 a.m., June 30, 1936, by Dr. J. S. McCartney of the University of Minnesota School of Medicine. There was no cyanosis or edema. Except for the heart there was little to be found besides intense acute congestion of the spleen which weighed 275 gm., of the liver which weighed 1525 gm., and of the kidneys which were not enlarged. The lungs presented no evidence of congestion or edema.

Gross Description of the Heart. The pericardial sac measured 15 cm. in its transverse diameter. The heart appeared to be enormous. When emptied of blood it weighed, however, only 275 gm. Even upon superficial inspection it was evident

that the great size of the organ was due to tremendous dilatation of its right chambers. Externally the right ventricle appeared to be moderately enlarged, but what seemed to be the right auricle was a very dilated, thin-walled chamber which obviously encroached upon the right ventricle. Its inferior and posterior walls were especially thin. The venae cavae were in their normal positions with respect to the right auricle, which formed the right one-third of the anterior surface of the heart; the pad of fat about 3.5 cm. in diameter and about 1.0 cm. in its thickest part. The left ventricle and auricle were both relatively small, and the former occupied very little of the anterior surface of the heart and practically none of the apical portion. The mouths of the pulmonary veins were not present in the specimen after removal from the body, but it was certain that they occupied their usual position. The aorta and pulmonary artery were joined with their proper ventricle and were in normal relation to each other. The auricular appendages were in their normal positions.

After opening the heart in the usual manner it was seen that both the right auricle and ventricle, especially the former, were greatly dilated and that the tricuspid valve was displaced and malformed. The left auricle and ventricle were comparatively small but appeared normal. The two coronary arteries, which were pliable and smooth-walled, had their usual origin. The circumflex branch of the right passed obliquely downward and toward the right on the anterior surface of the heart and then toward the left to the very inferior edge of the heart, forming a semicircle. This apparently anomalous location was due to the great enlargement of the right auricle, which formed the right one-third of the anterior surface of the heart; the vessel was actually in its normal location in relation to the right auricle and ventricle. The left coronary artery divided as usual into the anterior interventricular artery and the left circumflex artery. The latter ended in two large branches, one on the lateral wall of the left ventricle which ran obliquely anteriorly and downward from the posterior junction of the auricles and the ventricles; and another which ran downward from this point toward the lower edge of the heart on the posterior wall of the right ventricle and apparently represented the posterior interventricular artery, although it did not lie in the posterior interventricular sulcus.

The aortic valve appeared normal and measured approximately 5.0 cm. in circumference. The membranous portion of the interventricular septum was quite small, the muscular portion reaching almost up to the base of the aortic valve. The mitral valve had its normal structure and its normal chordae tendineae and papillary muscles. The mitral orifice was about 9.0 cm. in circumference. The thickness of the left ventricle near its base was 1.0 cm. The depth of this ventricle was 7.0 cm. The endocardium of the left auricle and ventricle appeared normal, as did their musculature.

The right side of the heart presented a very anomalous appearance and was a typical example of Ebstein's disease (figures 3 and 4). By far its greater part functioned as the auricle, since the tricuspid valve was displaced down into the ventricle, its line of attachment passing around the wall of the ventricle in a vertical direction instead of transversely between the auricle and the ventricle, dividing the ventricle into a proximal auricular two-thirds and a distal one-third which functioned as a ventricle. However, the true auricle and ventricle were joined as normally at the annulus fibrosus, which ran transversely, and the true auriculoventricular orifice was wide open and actually dilated. There was a very definite Eustachian valve in its normal location; and the coronary sinus was in its normal situation below this, although it did not have a Thebesian valve. The fossa ovalis was at its normal site but was patent; there was a thick fold in the left auricle across the foramen ovale, which was open at the top. This fold apparently made closure of the foramen fairly competent except for a small fenestrum in the lower part of the fold. The pectinate muscles of the right auricle were normal and had their origin at the annulus fibrosus.

The auricle bulged far out and its wall was translucent and composed almost entirely of connective tissue. The central fibrous body was in its normal position.

The anterior papillary muscle of the right ventricle was displaced from its usual site downward and forward toward the very apex and lay in the functional right ventricle beneath the displaced tricuspid valve. The tricuspid valve formed a

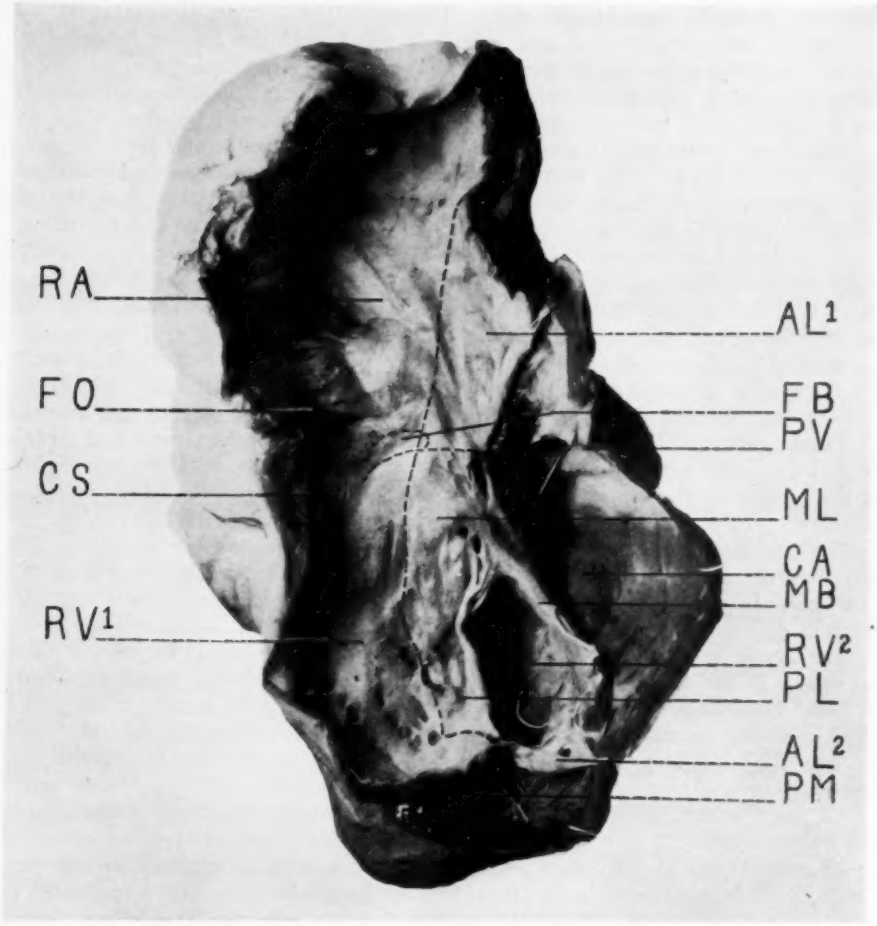

FIG. 3. Open right auricle and ventricle: RA, true right auricle; FO, foramen ovale; CS, coronary sinus orifice; RV^1, auricular portion of right ventricle; AL^1, anterior leaflet of tricuspid valve (main portion); FB, central fibrous body (oval in broken line); PV, pulmonary valve; ML, medial leaflet of tricuspid valve; CA, conus arteriosus; MB, moderator band; RV^2, functional right ventricle; PL, posterior leaflet of tricuspid valve; AL^2, anterior leaflet of tricuspid valve (lower end); PM, papillary muscle (not visible). Vertical broken line indicates line of attachment of tricuspid valve; horizontal broken line indicates true auriculoventricular junction.

continuous fold around the interior of the right ventricle and could be divided only arbitrarily into three leaflets. The septal or medial leaflet was attached vertically to the upper half of the interventricular septum below and anterior to the central fibrous body. It had short broad chordae tendineae passing forward into the prominent moderator band. This leaflet passed downward to fuse without a definite line

of demarcation into the much dislocated posterior leaflet, the free edge of which was rounded and thickened but not apparently diseased. It was about 1.5 cm. wide, and its attachment was vertically downward along the middle of the interventricular septum toward the apex. On its septal surface it was attached to a small teat-like papillary muscle, and at its lower extremity it was attached directly on its under surface to the papillary muscle in the apical region of the ventricle already referred to. Near the apex it fused with the larger anterior leaflet. The latter was attached at its upper limit to the annulus fibrosus and anterior upper limit of the interventricular septum, being fused with the medial leaflet where one stout chorda tendinea also attached it to the upper portion of the moderator band. Its line of attachment

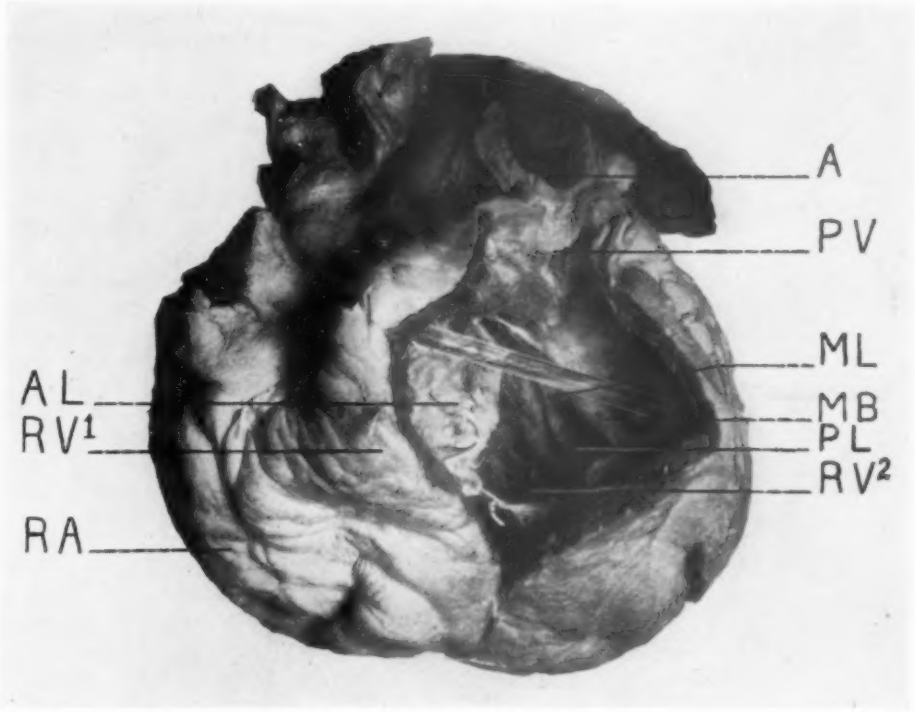

FIG. 4. Anterior view of right auricle and ventricle held open at anterior incision, looking into functional right ventricle, RV^2, and conus arteriosus to right of moderator band, MB. A, aorta; PV, pulmonary valve; ML, medial leaflet of tricuspid valve; PL, posterior leaflet of tricuspid valve; AL, anterior leaflet of tricuspid valve; RV^1, exterior of auricular portion of right ventricle; RA, exterior of lower portion of enlarged right auricle.

then passed down the anterior wall of the ventricle toward the apex where it fused with the posterior leaflet. It was roughly triangular and about 2.5 cm. wide in its widest portion. Its free edge was rounded and thickened like that of the posterior leaflet. It had a few delicate chordae tendineae attached to the under surface of its apical portion which fixed it lightly to the apical part of the ventricle, but its main attachment there was directly to the papillary muscle. The line of attachment of the whole valve measured about 12.0 cm.

The moderator band ran obliquely downward and forward from below the central fibrous body between the conus arteriosus and the small part of the right ventricle below and anterior to the displaced tricuspid valve. It formed a muscle

septum dividing the conus arteriosus from the functional right ventricle and was attached to the anterior part of the interventricular septum and the anterior wall of the conus. In its upper portion it was merely a trabeculum protruding from the interventricular septum, but in its lower half it was very broad, fan-shaped and thinner, and projected far out into the ventricular cavity and the conus.

The apical region of the ventricle beneath the tricuspid valve was a small chamber divided into two parts by the papillary muscle and a small muscular trabeculum joined to it. These spaces communicated with the small portion of ventricle between the valve and the broad moderator band by means of a cleft.

Histologic Study of the Heart. Two large blocks of tissue were excised from the heart which included most of the auriculoventricular septum and all of the interventricular septum. These blocks were imbedded in paraffin, and serial sections of 10 microns thickness were cut horizontally from above downward. All sections were mounted, and every fifth section down to section 670 of block 1 and every tenth section beyond that was stained with Masson's trichrome stain. There were 2820 sections made from block 1 and 1680 from block 2, making a total of 4500 sections. The auriculoventricular node and bundle were quite normal in structure and in their relationship to the true right auricle and the central fibrous body (figure 5). The division of the bundle of His into its two branches began at about section 490. On the right side of the interventricular septum the tricuspid valve was seen to be attached to the right of the middle in a vertical direction from above downward. The moderator band became more and more prominent as the sections descended, until in the lower part of block 1 it formed a high, moderately thin projecting muscular band at the anterior edge of the septum. The right bundle branch, normal in structure throughout its course, ran at first directly beneath the line of attachment of the septal leaflet of the tricuspid valve in a rather prominent small projection, surrounded on its peripheral and lateral sides by a fibrous rim and deeply by the septal musculature (figure 6). It changed in shape in its transverse section as it descended, becoming first fusiform, then roughly triangular and then oval. It gradually moved anteriorly from the middle of the septum, leaving the projection mentioned at about section 800 and moving toward the base of the moderator band which it reached at section 1060. It was subendocardial in this migration. The right bundle branch then gradually ascended along the posterior edge of the moderator band, lying beneath the anterior attachment of the septal leaflet as it ascended. The branch then gradually passed up to the unprotected summit of the moderator band which it reached at about section 2500, becoming a little deeper with a small rim of myocardium between it and the endocardium (figure 7). Below the middle of the interventricular septum in block 2 the moderator band became divided gradually from summit to base by a cleft, and the right bundle branch gave components to the two parts, spreading out broadly beneath the endocardium along the adjacent sides of the cleft and finally in the upper third of the block losing its identity (figure 8). The trabeculae carrying the bundle branch were at the base of the fan-like expansion of the moderator band.

The left bundle branch appeared quite normal in structure and location throughout its course beneath the endocardium covering the left side of the interventricular septum (figures 5, 6, 7 and 8). It gradually spread out to become broader and broader. About the middle of the septum it became definitely thicker in parts and began to divide into anterior and posterior divisions, which passed down toward the base of the anterior and posterior papillary muscles respectively and finally lost their identity in the lower part of the septum.

The endocardium and myocardium presented no evidence of ancient or recent inflammation, except for a small mass of fibrous tissue in the myocardium at about the middle of the septum and near its right ventricular surface, and changes in the wall of a moderately large intraseptal artery in the same general locality. These changes were suggestive of, but not pathognomonic of ancient rheumatic arthritis. Practically all other arteries appeared quite normal.

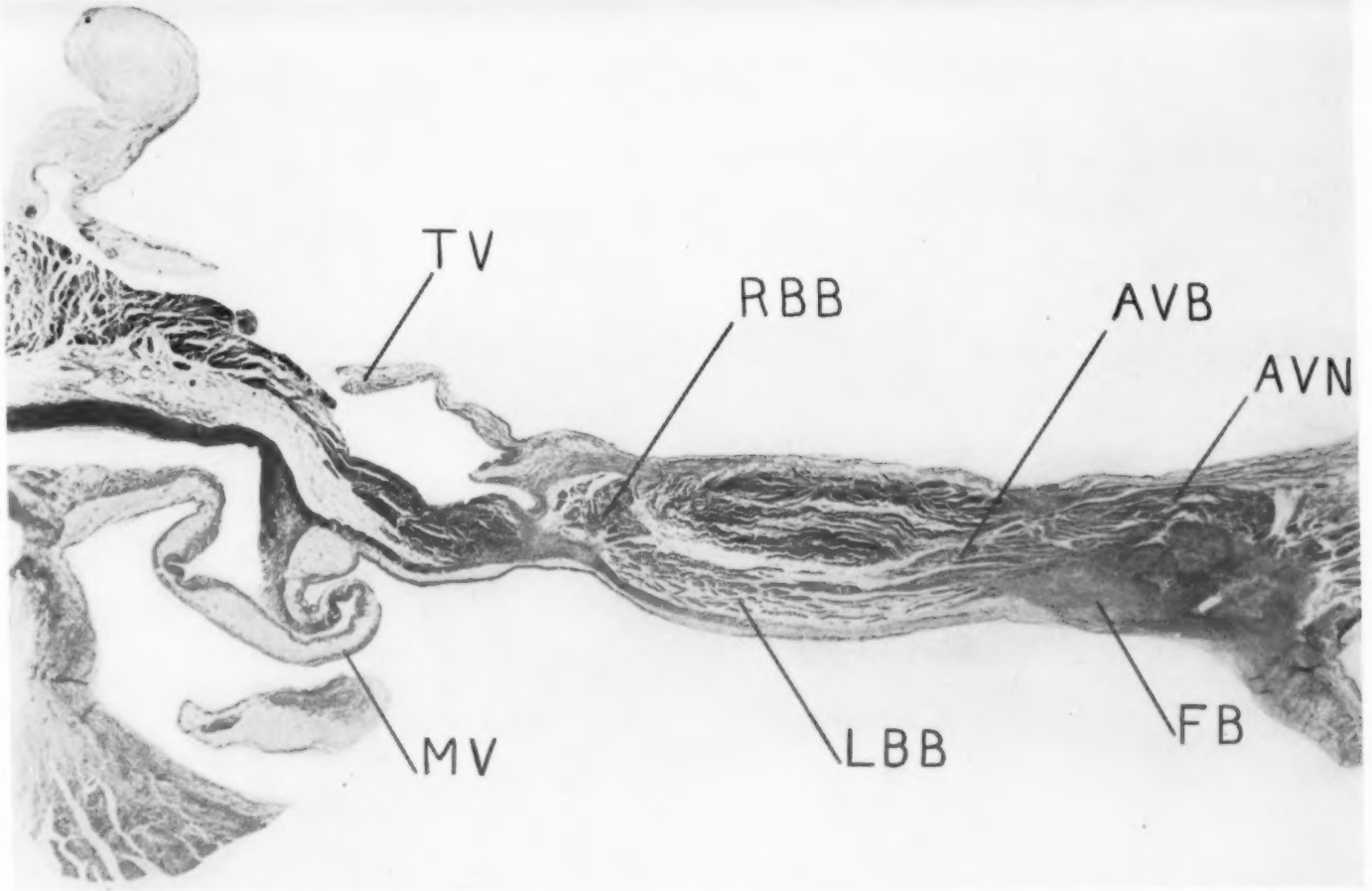

FIG. 5. Horizontal cross section of upper portion of interven ricular septum (block 1, section 485) : TV, tricuspid valve (medial leaflet) ; RBB, beginning of right bundle branch; AVB, auriculo ventricular bundle; AVN, auriculoventricular node; MV, mitral valve; LBB, beginning of left bundle branch; FB, central fibrous body. Reduced from a magnification of 10 times.

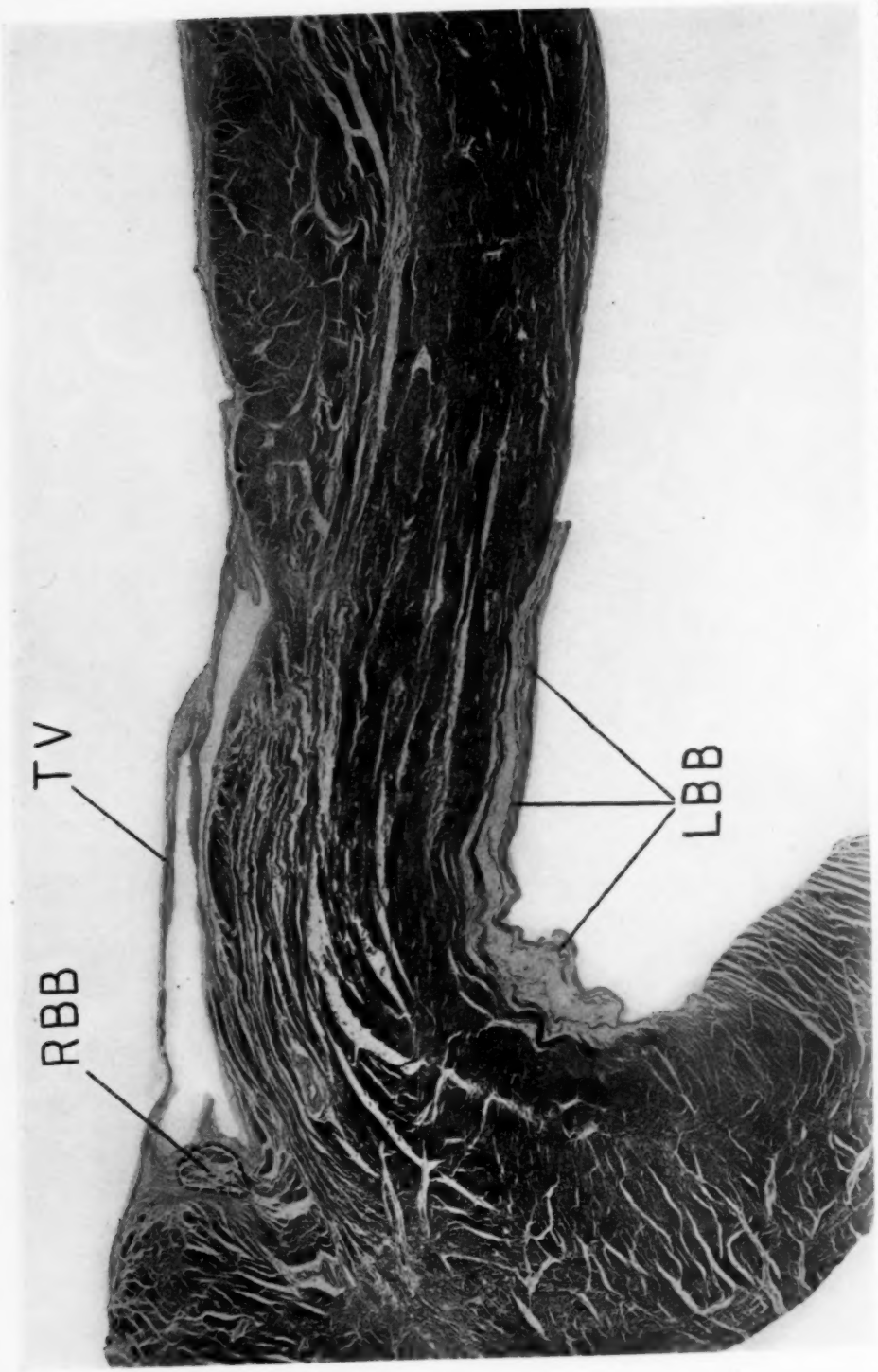

FIG. 6. Horizontal cross section of interventricular septum, upper third (block 1, section 1470): RBB, right bundle branch; TV, tricuspid valve (medial leaflet); LBB, left bundle branch. Reduced from a magnification of 10 times.

valve (medial leaflet); LBB, left bundle branch. Reduced from a magnification of 10 times.

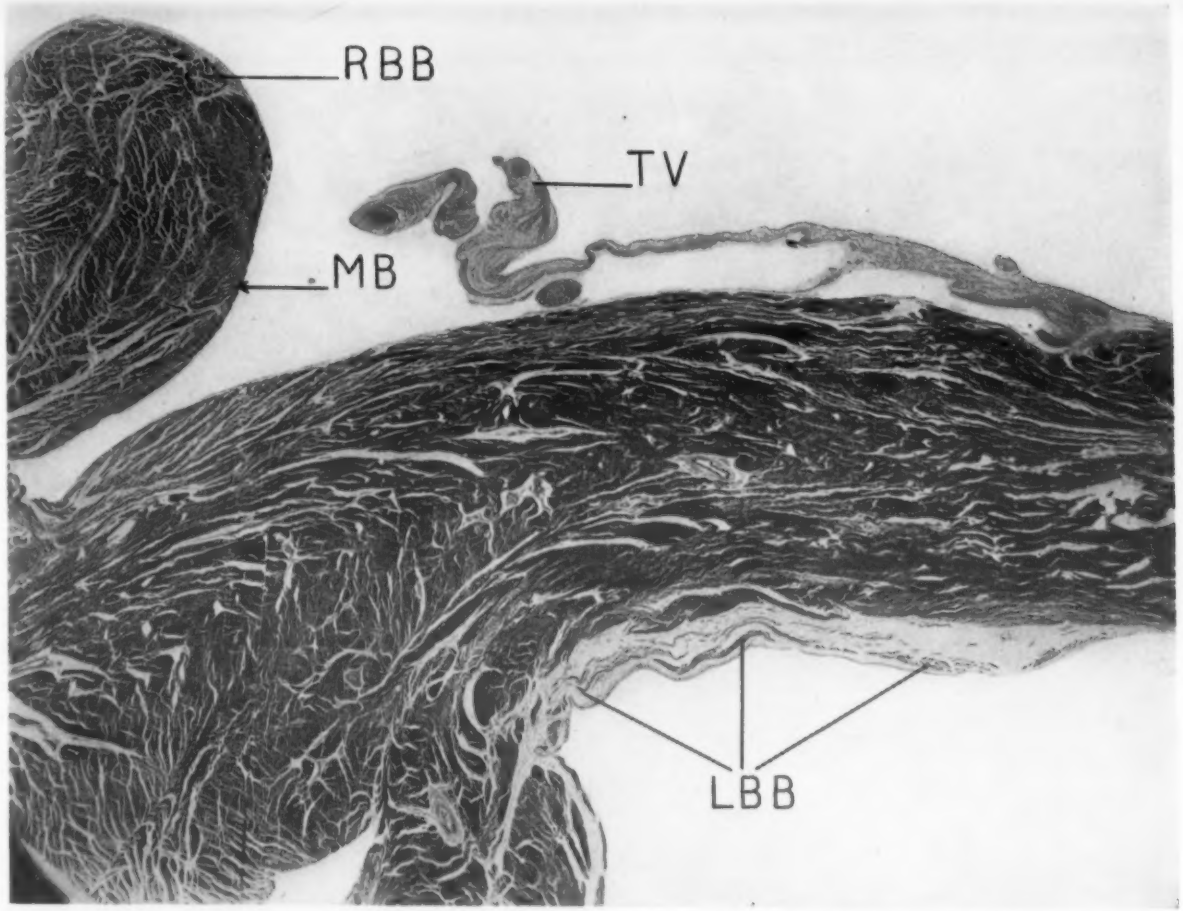

FIG. 7. Horizontal cross section of interventricular septum, about middle (block 1, section 2430): RBB, right bundle branch; MB, moderator band; TV, tricuspid valve (posterior leaflet); LBB, left bundle branch. Reduced from a magnification of 10 times.

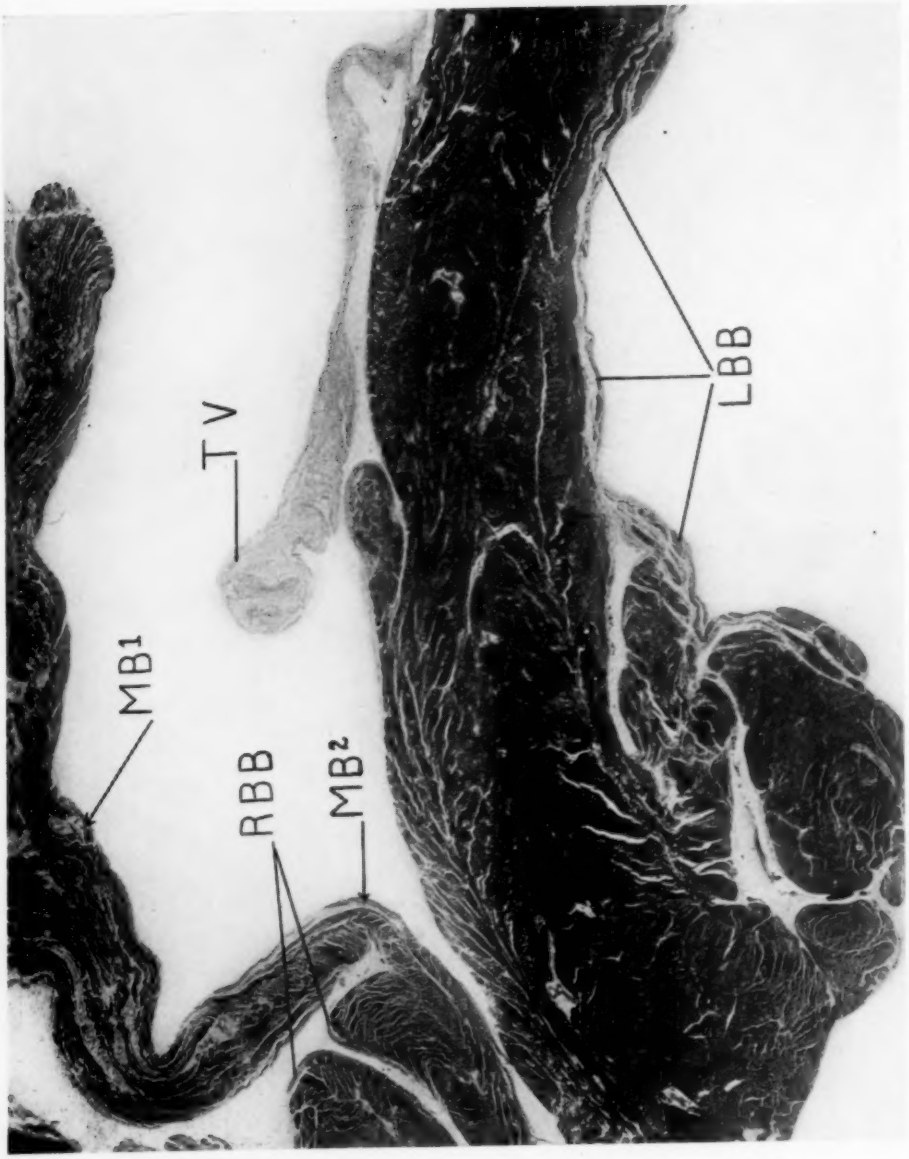

FIG. 8. Horizontal cross section of interventricular septum, lower middle third (block 2, section 310); MB^1, fan-like broadening of moderator band; RBB, right bundle branch, terminal expanded portion; MB^2, true moderator band; TV, tricuspid valve (posterior leaflet); LBB, left bundle branch. Reduced from a magnification of 10 times.

Discussion of Case

The case was a typical example of Ebstein's disease. Congenital heart disease was diagnosed, but the type of malformation could not be determined before death. The electrocardiographic abnormalities suggested left bundle-branch block (new terminology), and it had been hoped that the histologic study would show definite evidence that would aid in settling the controversy now waging concerning the terminology of intraventricular block. However, the left bundle branch was entirely normal, and although the course of the right bundle branch was somewhat abnormal it conformed in a general way to that of the normal heart, and the branch was not interrupted at any part of its microscopically recognizable portion. One must conclude, therefore, that the electrocardiogram can not definitely be designated as that of bundle-branch block but rather of left axis deviation due perhaps to an electrical imbalance between the right and left ventricles associated with prolongation of intraventricular conduction time.

Of the cases described in the literature this case seemed to resemble most closely that of Arnstein. The components of the three leaflets were fused and continuous, and it was impossible to say exactly what their limits were. The valve was obviously incompetent, and tricuspid regurgitation must have occurred. However, the extracardiac signs of this dysfunction were lacking because of hemodynamic properties which will be discussed later.

Comparison of Cases

The 16 cases of Ebstein's disease were similar in their fundamental nature, namely, the displacement of the valve downward into the right ventricle. In all, the anterior leaflet was partly attached to the annulus fibrosus, whereas the posterior leaflet had usually very little connection with it, and the medial or septal leaflet was attached to it in some cases and not in others. In almost all of the cases the anterior leaflet was much larger than the other leaflets. In some cases the septal leaflet appeared as an isolated, almost functionless flap attached to the interventricular septum, and in others it was an integral part of the whole valve. In some, the valve resembled a flapping sail, whereas in others, as in our case, it did not give that impression because the leaflets, especially the anterior, were either not so large or were more closely held by chordae tendineae and papillary muscles to the ventricular wall. There was considerable variation in the number, size and position of the papillary muscles and chordae tendineae. In some there were both present; in others there were mainly only papillary muscles or only chordae. The so-called moderator band, which in the human heart is usually poorly developed, was frequently much enlarged.

The amount of the ventricular cavity proximal and distal to the valve varied, but the distal portion was usually much smaller than the proximal, a condition which was exaggerated by the usually great dilatation of the so-called auricular portion of the ventricle. The degree of dilatation proximal to the valve, as well as the thinness of the wall, was apparently determined by the amount of regurgitating blood and possibly by the length of life. In all of the cases the true auriculoventricular ostium was enlarged, but there was considerable variation in the position, form and size of the actual valvular orifice between the auricular portion of the ventricle and the remainder of the ventricle, which consisted

of 10 times.

mainly of the conus arteriosus. In all of the cases it appeared probable that the valve was incompetent to close its orifice completely, thus allowing regurgitation. In one case, at least, there was also definite stenosis of the orifice. There was considerable variation in regard to accessory fenestra of the leaflets. The pulmonary conus varied moderately in size and in the thickness of its wall, and there were also variations of a relatively minor nature in the pulmonic valve.

Associated cardiac anomalies were of minor nature. The most common and most important was the patency of the foramen ovale, but this was not present in all cases. It was undoubtedly secondary to the increased pressure in the right auricle. The amount of blood flowing through it into the left auricle was not sufficient in most cases to cause appreciable enlargement of that chamber, since there was probably a diminished amount of blood flowing into the left auricle from the pulmonary circulation. There was considerable variation in the Eustachian and Thebesian valves, and when well developed they were probably of some importance in preventing the back flow of blood into the venae cavae and the coronary sinus.

The split posterior mitral leaflet in one case was of interest, but only as an associated anomaly.

The thickened endocardial plaques and the thickenings of valve leaflets and chordae tendineae in a few of the cases were probably only incidental.

Explanation of the Anomaly

Opinions have varied as to the cause of the anomaly. A few authors have attached great importance to intra-uterine endocarditis, but this, when it occurs, is probably only incidental and due to the predisposition of such malformed parts to inflammation. The most plausible explanation seems to be that of MacCallum,[4] who states: "The valves are, of course, formed on the medial side by a prolongation of the septum intermedium, on the lateral side by an involution of the wall of the auricular canal. If in an early stage these endothelial cushions reach a greater extent than normal and retain their attachment to the muscular trabeculae, they would in time become a membrane, supported by muscular trabeculae. This might occur only on the lateral side, the valves produced from the septum developing in part normally. The free edge has possibly lost its muscular attachment as a result of the inefficiency of muscular action in the direction in which the blood stream affects it."

The malformation occurs only in the otherwise essentially completely developed heart and probably before the eighth week of fetal life. According to Mall the posterior leaflet develops independently from the posterior wall of the endothelial tube, while the others originate from the endothelial cushions. In Ebstein's disease the posterior leaflet is the most anomalous, while the medial leaflet, though deformed, has always the most normal parts. Heigel believes that the usual large size of the anterior leaflet may be due to a compensatory effort.

Clinical Features

It would appear to be impossible to make the diagnosis of Ebstein's disease during life. The type of enlargement of the heart is not characteristic. There

may be both systolic and diastolic murmurs, with or without a thrill, but more often there is only a long, loud systolic murmur of greatest intensity in the third and fourth intercostal spaces close to the left border of the sternum. The pulmonic second sound is usually not accentuated.

Cyanosis and clubbing of the fingers may or may not be present. The presence of cyanosis depends, of course, upon the amount of venous blood flowing into the left auricle through the foramen ovale and the degree of diminution of the flow of blood into the pulmonary artery. The amount of cyanosis in one case decreased near the end of life, probably because the failing right ventricle ejected less venous blood through the foramen ovale.

The signs usually associated with tricuspid insufficiency, such as positive venous pulsation in the neck and pulsating liver, occur usually only when heart failure is precipitated by some serious infection, probably mainly because of the great enlargement of the right auricular portion of the heart, which acts as a reservoir, and partly in most cases because of the patency of the foramen ovale. The musculature of the auricular portion of the right ventricle is frequently practically absent, so that this portion of the ventricle plays little part in propelling blood up toward the true auricle.

The condition is compatible with long life, and death from heart failure alone is not the rule. Three patients died unexpectedly. The occurrence of pulmonary tuberculosis in four of the cases is interesting, showing perhaps an increased susceptibility of the lungs because of their reduced blood supply, as in cases of pulmonary stenosis.

Retarded development in the early years of life was noted in several cases, but usually after puberty growth was speeded up. In one case menstruation did not occur, and the uterus was found to be hypoplastic.

Other Examples of Congenital Tricuspid Insufficiency

Ebstein's disease is not the only cause of congenital tricuspid insufficiency. As other interesting examples we should like to refer to the cases of Hotz and of Ariel. Hotz [14] reported two very similar cases, one a girl who died at the age of 13 years, the other a boy who died at 12. In both cases there was cyanosis. In both the heart was enlarged, with accentuation of the pulmonic second sound, and roentgenograms showed marked enlargement in the region of the pulmonary conus. In one there was a variable soft systolic murmur; in the other there was no murmur, but toward the end paralysis of the left recurrent laryngeal nerve and diminution of the left radial pulse developed due to pressure upon the nerve and the aortic arch by the greatly enlarged pulmonary artery and right auricle. Death was due to heart failure with tricuspid insufficiency in both cases. Necropsy revealed that the tricuspid valve had only two short leaflets in one and one well developed and two rudimentary leaflets in the other.

In Ariel's [15] case a cyanotic male infant died after two days. There were lobar pneumonia and passive congestion of all of the organs. Both the mitral and tricuspid valves were represented by tumor-like processes which were interpreted as congenital overgrowths or hyperplasia of the embryonic connective tissue of the endocardial cushions. Microscopic sections showed these anomalous valves to consist of avascular, thick collagen fibers.

SUMMARY

Ebstein's disease of the heart is a rare congenital malformation consisting essentially of downward displacement of the tricuspid valve in an otherwise completely developed heart. The right auricle is greatly enlarged, and the foramen ovale is usually patent. The true right auriculoventricular ostium is enlarged. The tricuspid valve is obviously incompetent, but venous congestion and pulsation do not occur unless an additional strain or damage precipitates heart failure. The condition is not incompatible with long life. Pulmonary tuberculosis is a common complication, probably because of reduced pulmonary blood flow. The lesion may be suspected with other possibilities but can not be positively diagnosed during life.

The sixteenth case is reported. The patient was a woman aged 21 years who was known to have a congenital heart lesion and who died unexpectedly. Necropsy revealed only the heart lesion and acute congestion of the viscera. The electrocardiogram had revealed left axis deviation and prolonged intraventricular conduction time. Histologic study of the conduction system by means of 4500 serial sections did not reveal any significant lesion, although the course of the right bundle branch was somewhat anomalous.

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EDITORIAL

THE INCIDENCE OF TRICHINOSIS

Hall and Collins[1, 2, 3] have recently reported a study of 300 human diaphragms from autopsy cases in 10 hospitals in Washington, D.C., and from one hospital in Baltimore which showed that trichinae were present in 13.67 per cent. This figure seems surprisingly high but as Hall points out this is only because we look upon human trichinosis as a rare disease. Previous investigators in different parts of the country have all agreed that latent trichinosis as evidenced by infestation of the diaphragm with trichinae is to be found in a significant percentage of the population. A tabulation of earlier investigations shows percentage incidences found in different sections of the country ranging from 3.5 per cent in New Orleans to 27.6 per cent in Boston. In general the highest incidences were found on the east and west coasts and the lowest in the far south.

This geographic variation the authors are inclined to attribute chiefly to garbage and swill feeding of pigs near the large eastern and western population centers whereas in the south it is more usual for swine to run free in the woods and forage for themselves. In swill and garbage pork scraps are found and such scraps containing trichinae perpetuate the disease in swine. The eating by hogs of trichinae infested rats is a less frequent cause. Both Hall and Schwartz in separate studies showed that live trichinae are far more frequently found in garbage-fed than in grain-fed hogs. The incidence in garbage-fed hogs was 4.8 to 5 per cent and in grain-fed hogs 1 to 1.5 per cent. It is of interest to note that trichinae are to be found far more frequently in the human than in the porcine inhabitants of the United States.

The above data as to geographic variations of incidence in man are not to be accepted as conclusive. The number of cases studied and the methods employed in their study have been too variable to warrant entire confidence in any statistical interpretations. Hall and his coworkers believe, however, that few errors are made in the interpretation of the finding of encysted living or dead trichinae since these are easily recognized; but they feel that unless two or more methods are used many positive cases will be overlooked. In their studies they made a direct microscopic examination of one gram of diaphragm muscle pressed flat between heavy glass plates. In addition varying amounts, averaging 113 grams, of diaphragm were digested in artificial gastric juice for approximately 24 hours and the re-

[1] HALL, M. C., and COLLINS, B. J.: Studies on trichinosis: 1. The incidence of trichinosis as indicated by postmortem examination of 300 diaphragms, Public Health Reports, 1937, lii, 468–490.

[2] HALL, M. C.: Studies on trichinosis. III. The complex clinical picture of trichinosis and the diagnosis of the disease, Public Health Reports, 1937, lii, 539–551.

[3] HALL, M. C.: Studies on trichinosis. IV. The rôle of the garbage fed hog in the production of human trichinosis, Public Health Reports, 1937, lii, 873–886.

sultant mixture poured on the screen of a Baermann apparatus. The water coming through as well as the material on the screen were examined for trichinae. The microscopic press-preparation was found most valuable for detecting encysted dead larvae while live larvae were more readily discovered by the digestion-Baermann method. The authors believe that only through semi-quantitative methods applied to very large series of cases in different localities can we obtain a more accurate picture of the prevalence of this potentially serious condition.

In the various reports on the incidence of trichinosis in the United States as determined by postmortem studies of the diaphragmatic muscle Hall found 222 positive cases reported. He was unable to find evidence that a diagnosis of trichinosis had been made in life in a single one of these 222 cases. One reason for this lack of recognition of the infestation may be that in a majority of the cases the number of larvae which entered the circulation and eventually became encysted in the muscles was too small to have caused definite clinical symptoms. It is not known of course whether the number of larvae per gram of diaphragmatic muscle is a dependable index of the concentration of larvae in other portions of the body. We do know that the diaphragm is uniformly attacked and usually contains a high concentration of trichinae. Hall's and Collins' careful work gives the number of trichinae per gram in each of their 41 positive cases. This number is found in their tabulation to vary between 0.006 and 993. In only two cases were there more than 100 trichinae per gram and in only 11 cases were there more than 10 per gram. In 14 cases the average number was less than 1 per gram. No information is yet available to indicate what degree of infestation is necessary to produce the clinical picture of trichinosis but it is probable, Hall and Collins feel, that cases with less than 1 trichina per gram of muscle present few symptoms, and that those with over 100 trichinae per gram show a clear cut clinical picture of trichinosis. Between these extremes there must occur many cases with mild or atypical symptoms which we do not at present associate with clinical trichinosis. There is here undoubtedly an unexplored clinical field. In addition to the symptoms now usually considered as cardinal—gastrointestinal disturbances, fever, suborbital edema, painful muscles, pneumonia—we must learn to suspect of trichinosis infestation cases showing certain ocular lesions, atypical myocardial involvement, meningismus, encephalitis with stupor, diaphragmatic pleurisy, urticaria, etc. The search for eosinophilia, the biopsy of muscle, the search for trichina larvae in the blood and cerebrospinal fluid, the skin test and the precipitin test should be applied more freely in our clinical investigations of obscure disease processes.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume XII: Preventive Medicine and Hygiene.* Associate Editor: IRA V. HISCOCK, M.A., C.P.H., Professor of Public Health, Yale University School of Medicine. xxxviii + 993 pages, 45 illustrations. D. Appleton-Century Company, Inc., New York. 1937. Price, $10 a volume.

The previous eleven volumes of *The Practitioner's Library* have been reviewed in the ANNALS as they have appeared. The twelfth volume, *Preventive Medicine and Hygiene,* is an interesting and valuable addition to the set. Twenty-five authors, each chosen for special knowledge of some particular field, have contributed the forty-two chapters. The associate editor, Ira V. Hiscock, has himself provided nine chapters. The subject matter is grouped into four parts of which Part I deals with Individual Hygiene. Of special interest to the general practitioner are the chapters in this section on General Considerations Concerning the Periodic Health Examination by Haven Emerson and on The Content and Technics of Periodic Health Examinations by Harold S. Diehl. The benefits of an annual or semi-annual health audit so overwhelmingly outweigh the arguments against this procedure that the practitioner must be prepared to meet an increasing demand for this form of service. Unless the periodic examination is conducted in a thoroughly scientific manner and its results properly recorded by some such method as described in these chapters, its value may be lost and the procedure fall into disrepute. The practitioner will find these chapters full of practical suggestions applicable to his routine examinations of sick people as well as of those who are presumptively in a state of health. The chapter on Sex Hygiene by M. J. Exner and W. F. Snow is especially valuable. In it the practitioner will find safe and reasoned answers for the many questions which are asked him about juvenile sexuality, masturbation, continence and sex-adjustment in marriage. Part II is devoted to Group Hygiene and will prove of special use to the physician who is the health advisor to a rural community. The hygiene of the home and of educational institutions and the health hazards of farming are topics which are fully developed. Part III deals with Community Health and here will be found basic information on the protection of food and water supplies and on sewage disposal. In the smaller communities the physician is frequently called upon to advise or even direct in such matters. Likewise the control of communicable diseases in general, and of tuberculosis and the venereal diseases in particular, is discussed here. Part IV covers The Prevention of Specific Diseases. The chapter on Prevention of the Infectious Diseases is by William H. Park and Morris Seigel; those concerned with Toxic and Physical Agents by Emery R. Hayhurst. It is impossible, in a limited review, to refer specifically to each of the chapters treating of prevention of disease in various anatomical systems. As the reviewer has had occasion to write in regard to preceding volumes, this series is remarkably free from typographical errors for a first edition. There is an unavoidable variance in literary style and an occasional lapse into medical slang which is out of harmony with the dignity of the work as a whole. Should we be alarmed or relieved that (p. 853) "The mortality in the best clinics is from 2 to 8 per cent of all prostates who enter," or that (p. 855) "The future of the testicular tumors is always in doubt"? The nice press work and adequate indexing which have been found in previous volumes are maintained here. This twelfth volume is a worthy addition to the *Library,* and fully qualified to stand alone as an adequate textbook of Preventive Medicine and Hygiene.

C. V. W.

Orthodiascopy. By CHESTER M. KURTZ, M.D., F.A.C.P., Assistant Professor of Medicine, University of Wisconsin; Cardiologist to the State of Wisconsin General Hospital. 247 pages; 15 × 22 cm.; indexed. The Macmillan Company, New York. 1937. Price, $3.50.

The author describes the technic of recording orthodiagrams and the apparatus necessary. The normal cardiac silhouette is depicted and in subsequent chapters alterations from normal in size and silhouette due to the various diseases of the heart are discussed. The author's observations indicate that the method of determining the frontal area of the heart described by Hodges and Eyster gives the most reliable evidence of cardiac enlargement and nomograms for determining the expected (normal) frontal area are presented. The author holds that the combination of fluoroscopy and orthodiascopy is the most valuable roentgenologic method of examining the heart and recording its size and contour. With this point of view the reviewer is in entire accord. However, no roentgenologic method as yet devised gives infallible evidence as to whether lesser deviations from an expected normal mean cardiac enlargement. Such decisions ultimately must be based not on measurements alone but on other considerations as well. It is only fair to state that the author recognizes this fact in spite of his enthusiasm for the methods described. It would have been wise to have stressed it more. For many reasons it would seem obvious that the cardiologist is the logical person to perform such examinations. This book is recommended to those interested in this subject.

W. S. L., JR.

Biological Time. By P. LECOMTE DU NOUY, Chief of the Division of Molecular Physics, Pasteur Institute, Paris; formerly Associate Member of the Rockefeller Institute. Foreword by Alex Carrell, M.D. ix + 180 pages; 20 × 12.5 cm. Macmillan Co. New York. 1937. Price, $2.00.

This interesting volume is divided into three main headings. The first, entitled "The Biological Problem and Methods," compares the methods of the physical scientist with those of the biologist and in it the limitations of physical methods in biology are emphasized.

The second division of the book is entitled, "Cicatrization of Wounds and Tissue-Culture." In this a comprehensive survey of the cicatrization of wounds on individuals of various age groups is reported. Many of the observations of the author were made on soldiers during the World War. The rapidity of healing in the young and the delayed cicatrization in late life are clearly demonstrated. Many diagrams are included illustrating these phenomena. Further work in this section is reported on the speed of cicatrization with respect to the area of the wound. Several curves expressing this relationship in various wounds are given and a general exponential equation giving mathematical expression to the subject has been developed.

Part three is entitled, "Time." Much space is given to a consideration of the idiology of time as one of the spacial dimensions. Man's concept of time was plotted against his age and interestingly enough the hyperbolic curves obtained by the plotting of man's concept of the time against age and wound cicatrization against age coincide. Finally the author questions whether quantitative symbols will ever express life or psychological phenomena in general—for mathematics cannot express the beauty life so often embodies.

This book should capture the imagination of the scientifically minded physician.

J. C. K., JR.

The Postmortem Examination. By SIDNEY FARBER, M.D., Associate in Pathology, Harvard Medical School. 201 pages; 16 × 23.5 cm. Charles C. Thomas, Springfield, Ill. 1937. Price, $3.50.

Beginning with a brief historical introduction which sketches the influence of the necropsy upon clinical medicine, this manual proceeds with a detailed consideration of the methods employed in the systematic postmortem examination. The clinical methods of Virchow and Rokitansky are used as the basis of the discussion with alternative procedures mentioned when indicated. The exposition is detailed and clear. Helpful illustrations are included from time to time. A brief reference to the problems presented by the medico-legal postmortem is given, but the reader is referred to other sources for more complete information. Because of the author's experience, the section devoted to necropsies on infants and children is of especial interest. Included also are helpful tables of average weights of organs in both adults and children. An adequate index is presented. The book can be heartily recommended as a useful guide for the neophyte and one which points the way toward a high standard of excellence in the performance of the postmortem examination.

M. S. S.

William Withering: The Introduction of Digitalis into Medical Practice. By LOUIS H. RODDIS, M.D.; Commander, Medical Corps, U. S. N. 131 pages; 14 × 19.5 cm. Paul B. Hoeber, Inc. New York. 1936. Price, $1.50.

The reviewer has not previously read a biography of William Withering, and indeed no other seems to be extant. The author's source material is revealed in the appendix and includes the memoir by Withering's son. One does not gain a very adequate impression of the personality of the man from this biography, but this is doubtless due to the lack of material from which to draw such a picture rather than to any fault of the author. We do see Withering to be a man interested in many scientific pursuits as so many were in his time. We find him to be a botanist of note, a mineralogist, a student of climatological phenomena and an observing clinician. He was interested in the social movements of his day and was a sympathizer with the French Revolution. His medical fame has a secure base in his observations on digitalis. This drug was first brought to his attention in 1775 as a "family recipe for the cure of dropsy." With his botanical knowledge it was not difficult for him to discover that the foxglove was the active ingredient. The author quotes frequently from Withering's writings and includes in the text the section of the book on digitalis dealing with: Preparation of the Drug; Effects, Rules and Cautions; Constitution of the Patients; Inferences. Although Withering attributed the therapeutic qualities of foxglove to a diuretic action, but little has since been added to his clinical observations.

W. S. L., JR.

Weight Reduction, Diet, and Dishes. By E. E. CLAXTON, M.B., B.S. (London), D. T. M. and H. 199 pages; 14 × 22 cm. William Heinemann (Medical Books) Ltd., 99 Great Russell St., London, W. C. I. 1937. Price, 8 s. 6 d. net.

This is a readable and useful book on the treatment of overweight, couched in language midway between vernacular and textbook. Endowed with British whimsy, and aimed for the use of the lay person, it proceeds with moderate pedagogical repetition at a slow and steady pace. There is an unusual plowing up of superstitions and a most serious discussion of the disadvantages of being fat. The "banana and milk" diet is properly expounded. An undue emphasis is put on salt and on the ductless glands which are dragged in as a sort of *deus ex machina* whenever the discussion seems to be getting out of hand. The recipes are abundant and explicit. They are unusual in that they make individual servings. It will be a useful handbook for coöperative patients, and an acceptable textbook for dieticians and students.

C. A.

COLLEGE NEWS NOTES

New Life Member: Dr. Louise Tayler-Jones (Fellow), McLean, Va., became a Life Member of the American College of Physicians on November 11, 1937.

Gifts to the College Library

Receipt is gratefully acknowledged of the following donations to the College Library of publications by members:

Books

Rear Admiral C. S. Butler (MC), U. S. N. (Fellow), Washington, D. C.—an autographed copy, "Syphilis Sive Morbus Humanus";
Dr. William Fitch Cheney (Fellow), San Francisco, Calif.—"The Diagnosis and Treatment of Diseases of the Stomach and Intestines";
Dr. J. C. Geiger (Fellow), San Francisco, Calif.—"Bacteriology of Specific Communicable Diseases: Handbook of Public Health Bacteriology";
Dr. Frank H. Krusen (Associate), Rochester, Minn.—an autographed copy, "Physical Therapy in Arthritis";
Dr. Aaron E. Parsonnet (Fellow), Newark, N. J., and Dr. Albert S. Hyman (Fellow), New York, N. Y.—"Applied Electrocardiography";
Dr. Bernard L. Wyatt (Fellow), Tucson, Ariz.—an autographed copy, "Chronic Arthritis and Fibrositis."

Reprints

Dr. Marcos Fernan-Nunez (Associate), Milwaukee, Wis.—"Medicine as a Career";
Dr. Fred M. F. Meixner (Fellow), Peoria, Ill.—"Treatment of Pneumonia";
Dr. Lewis J. Moorman (Fellow), Oklahoma City, Okla.—"Francis Adams of Banchory"; "Medicine Versus State Medicine"; "Multiple Calcifications in the Spleen"; "The Home Versus the Preventorium in the Management of Tuberculosis Contacts"; "The Tuberculosis Problem."

Acknowledgment is also made of the receipt of a report prepared by the Bureau of Medical Economics of the American Medical Association, entitled "Group Hospitalization."

Dr. Currier McEwen (Fellow), New York, N. Y., has been appointed Dean of the New York University College of Medicine. Dr. McEwen is thirty-five years of age, the youngest medical college dean in the United States. He graduated from New York University College of Medicine in 1926, and heretofore has been Assistant Professor of Medicine and Assistant Dean and Secretary of his Alma Mater.

Dr. David I. Abramson (Associate), formerly of Brooklyn, N. Y., has been appointed Director of Cardiovascular Research in the Institute for Medical Research of the Jewish Hospital, Cincinnati, Ohio, as of November 1, 1937.

Dr. S. A. Slater (Fellow), head of the Southwestern Minnesota sanatorium at Worthington, was elected president of the Minnesota Public Health association at the

annual meeting of that organization in St. Paul. He will assume office January 1, 1938.

Dr. August A. Werner (Fellow), St. Louis, Mo., gave two lectures under the auspices of the Iowa State Medical Society for their postgraduate course at Sheldon, Iowa, on November 1, and at Waterloo, Iowa, on November 2, his subject being "Gonad Hormones in Health and Disease."

The Tenth Annual Graduate Fortnight of the New York Academy of Medicine was held from November 1 to 12, 1937, and was devoted to "Medical and Surgical Disorders of the Urinary Tract." Dr. James Alex. Miller (Fellow and ex-President), is President of the Academy. On the Graduate Fortnight Committee appeared the names of the following Fellows of the College: Dr. Bernard Sutro Oppenheimer, Chairman; Dr. Ralph Henderson Boots, Dr. Thomas T. Mackie, and Dr. Herman O. Mosenthal.

Among presentations on the program were: Dr. James Alex. Miller (Fellow), Address of Welcome; Dr. George Baehr (Fellow), "The Pathology of Nephritis"; Dr. Robert F. Loeb (Fellow), "Clinical Aspects of Nephritis"; Dr. Herman O. Mosenthal (Fellow), "Clinical Aspects of Hypertension, Including Malignant Hypertension"; Dr. W. W. Herrick (Fellow), "Vascular and Renal Complications of Pregnancy."

The program of afternoon hospital clinics included presentations by the following Fellows: Dr. Soma Weiss (Boston), Dr. I. W. Held, Dr. William Goldring, Dr. Walter W. Palmer, Dr. Robert F. Loeb, Dr. George A. Sheehan, Dr. B. P. Stivelman, Dr. B. S. Oppenheimer, Dr. A. M. Master, Dr. Herman O. Mosenthal, Dr. Benjamin I. Ashe, Dr. Lewis A. Conner, Dr. C. E. de la Chapelle, Dr. W. W. Herrick, Dr. S. Edward King, Dr. Albert S. Hyman, Dr. Maximilian A. Ramirez, Dr. James R. Lisa and Dr. I. Seth Hirsch.

At the annual meeting of the California Section of the American Sanatorium Association, held at Orange, California, November 12, 1937, the following Fellows participated, Dr. E. W. Hayes (Fellow), acting as one of the hosts: Dr. H. G. Trimble, presentation of report on resolutions to the American Sanatorium Association and the National Tuberculosis Association; Dr. Chesley Bush, résumé of the present status of the Association of Thoracic Surgeons; Dr. F. M. Pottenger, follow-up program of cases discharged with a favorable result from the Tuberculosis Sanatorium; Dr. Chesley Bush (with Dr. Everett Morris), choosing a site for the new Tuberculosis Sanatorium; urban vs. rural locations; a division of the General Hospital or individual entity; Dr. Harold G. Trimble (with Dr. W. A. Hodges), the present place and future development of the Preventorium.

Dr. Edward J. Engberg (Fellow), St. Paul, Minn., has been appointed Superintendent of the School for Feeble-Minded at Faribault, Minn., by the State Board of Control.

Dr. Byrl R. Kirklin (Fellow), Rochester, Minn., Professor of Radiology in the University of Minnesota Graduate School of Medicine (Mayo Foundation), and Dr. Harry M. Weber received the first award for their exhibit at the International Con-

gress of Radiologists at Chicago during September. Dr. Kirklin was elected President of the Roentgen-Ray Society.

Dr. Thomas B. Magath (Fellow), Rochester, Minn., Professor of Parasitology in the University of Minnesota Graduate School of Medicine (Mayo Foundation), has been elected President of the American Society of Clinical Pathologists. Dr. Magath is the City Health Officer in Rochester.

Dr. Henry L. Ulrich (Fellow), Minneapolis, Minn., Professor of Medicine at the University of Minnesota Medical School, has been installed as President of the Hennepin County Medical Society.

Dr. J. Richards Aurelius (Fellow), St. Paul, Minn., and Dr. Louis E. Prickman (Associate), Rochester, Minn., have been elected Secretary and Treasurer, respectively, of the Alumni Association of the Mayo Foundation.

Dr. Horton Casparis (Fellow), Nashville, Tenn., Professor of Pediatrics, Vanderbilt University Medical School, and Dr. Julius H. Hess (Fellow), Chicago, Ill., Professor of Pediatrics, University of Illinois Medical School, were guest speakers on the postgraduate symposium on Diseases of Women and Children held at Duke University, Durham, N. C., November 11 to 13.

Dr. Douglas Martin (Fellow), Tampa, Fla., and Dr. Warren W. Quillian (Fellow), Coral Gables, Fla., have been elected President and Secretary, respectively, of the Florida Pediatric Society.

Dr. Oliver B. Kiel (Fellow), Wichita Falls, Tex., has been elected President of the Texas State Board of Medical Examiners.

Dr. Edgar M. Dunstan (Fellow), Dallas, Tex., has been appointed Superintendent of the Dallas City and County Hospital System.

Dr. Walter E. Vest (Fellow and Governor), Huntington, W. Va., has been elected President of the Public Health Council of West Virginia.

Dr. E. H. Shuller (Associate), McAlester, Okla., has been elected President of the Southeastern Oklahoma Medical Association.

Dr. Priscilla White (Fellow), Boston, Mass., was one of the guest speakers at a scientific meeting of the Georgia Pediatric Society at Atlanta, December 9.

Dr. Samuel A. Levine (Fellow), Boston, Mass., Professor of Medicine, Harvard Medical School, and Dr. Cyrus C. Sturgis (Fellow), Ann Arbor, Mich., Professor of Medicine and Director of the Simpson Memorial Institute for Medical Research, University of Michigan, were guest speakers on the program of the Oklahoma City Clinical Society's Conference, November 1 to 4, 1937.

The Twelfth Series of Friday Afternoon Lectures sponsored by the New York Academy of Medicine for 1937–38 is made up, in part, by the following: November 19, 1937—Dr. Robert L. Levy (Fellow), New York, N. Y.—"Drugs in the Treatment of Heart Disease"; December 17, 1937—Dr. Eugene M. Landis (Fellow), Philadelphia, Pa.—"Recent Advances in the Diagnosis and Treatment of Peripheral Vascular Diseases"; January 7, 1938—Dr. Rufus Cole (Fellow), Mount Kisco, N. Y.—"Treatment of Pneumonia"; February 18, 1938—Dr. William Thalhimer (Fellow), New York, N. Y.—"Convalescent Measles and Scarlet Fever Serums: Their Value in Prophylaxis and Therapy"; March 4, 1938—Dr. Milton A. Bridges (Fellow), New York, N. Y.—"The Evaluation of Recent Therapeutic Procedures"; March 11, 1938—Dr. Thomas T. Mackie (Fellow), New York, N. Y.—"Various Types of Colitis, with Particular Reference to Ulcerative Colitis"; March 18, 1938—Dr. James Ralph Scott (Fellow), New York, N. Y.—"The Modern Treatment of Diabetes Mellitus."

Dr. Edward S. Sledge (Fellow), President of the Alabama State Medical Association, addressed the Gulf Coast Clinical Society at Biloxi, Miss., on November 3 on "The Clinical Value and Limitations of Electrocardiography."

Other Fellows who contributed to the program were Colonel Charles F. Craig, New Orleans, La.; Dr. Horton R. Casparis, Nashville, Tenn., Dr. William C. Chaney, Memphis, Tenn.; Dr. Ray M. Balyeat, Oklahoma City, Okla.

Dr. Lewis M. Hurxthal (Fellow), Boston, Mass., was a guest speaker on the program of the Medical Institute of the University of Toledo on November 19, 1937.

Dr. Walter F. Donaldson (Fellow), Pittsburgh, Pa., has been reëlected Secretary of the Medical Society of the State of Pennsylvania.

Dr. Russell L. Haden (Fellow), Cleveland, Ohio, and Dr. William D. Stroud (Fellow and Treasurer), Philadelphia, Pa., were among the guest speakers on the program of the Post-Graduate Medical Assembly of South Texas, at Houston, November 2 to 4.

The Annual Congress of the Pan American Medical Association will be held January 15–31, 1938, aboard the S. S. Queen of Bermuda, on a cruise to Havana, Port au Prince, Trujillo City and San Juan. Among chairmen of sections are the following: Colonel Charles F. Craig (Fellow), New Orleans, La.—"Tropical Medicine"; Dr. Jay A. Myers (Fellow), Minneapolis, Minn.—"Thoracic Section"; Dr. Howard R. Hartman (Fellow), Rochester, Minn.—"General Medicine"; Dr. Edwin

C. Ernst (Fellow), St. Louis, Mo.—"Radiology"; Dr. Orville E. Barbour (Fellow), Peoria, Ill.—"Pediatrics."

Dr. Henry A. Luce (Fellow), Detroit, Mich., is President-Elect of the Michigan State Medical Association.

Dr. Charles E. Sears (Fellow), Portland, Ore., is President-Elect of the Oregon State Medical Society.

Dr. Raymond G. Taylor (Fellow), Los Angeles, Calif., is President-Elect of the Radiological Society of North America.

Dr. Carleton B. Peirce (Fellow), Ann Arbor, Mich., is Secretary of the American Roentgen-Ray Society.

Dr. Walter C. Swann (Fellow), Huntington, W. Va., was elected President of the Cabell County Medical Society for the year, 1938.

Research Fellowships Available: Fellowships in the medical sciences for the year beginning July 1, 1938, have been announced by the National Research Council. Fellowships are open to citizens of the United States and Canada who have the degree of doctor of medicine or doctor of philosophy. The Fellowships are intended primarily for recent graduates, and not for persons already established professionally. Applications should be filed by January 1, 1938. Appointments will be made at a meeting of the Medical Fellowship Board about March 1, 1938. Additional information may be obtained from the Secretary of the Medical Fellowship Board, National Research Council, 2101 Constitution Avenue, Washington, D. C.

Regional Meeting of Virginia Members

A Regional Meeting of the Fellows and Associates of the American College of Physicians residing in Virginia was held, in connection with a Banquet, at the Shenandoah Club, Roanoke, Va., October 12, 1937, with twenty-six members present.

The Virginia members have organized their group under a local President and Secretary. Dr. J. W. Preston, of Roanoke, was elected President of the local chapter to succeed Dr. W. B. Martin, and Dr. George B. Lawson, of Roanoke, was elected Secretary to succeed Dr. F. C. Rinker.

There was a general discussion concerning the present method of distributing inquiry cards to all Fellows concerning new candidates. The By-Laws of the College, Article V, Section 2, after covering the method by which a candidate shall be nominated, states "Further, the name of the candidate shall be sent to each Fellow in the candidate's locality, with a request for comments as to the candidate's fitness." This has been accomplished through cards sent out from the Office of the Executive Secretary after the receipt of each proposal.

A resolution was adopted referring to the Board of Regents, through the Executive Secretary, the recommendation that this system be changed, and in its

place a system adopted whereby regional committees shall be appointed, consisting of about four or five members, located in different sections of each state, whose duty it shall be to investigate and reply to all letters of inquiries in regard to eligibility of new members.

A further resolution was adopted that the Virginia Chapter of the College hold two regional meetings per annum, one at the Medical College of Virginia, in Richmond, and the other at the University of Virginia, at Charlottesville.

Corrections, 1937 Directory

It is regretted that two errors have been made in the names of Fellows of the College in connection with our biographical listing in the 1937 Directory. It is requested that members of the College reading this notice will kindly record these corrections in their directories:

Page 386, Jordan, Sara Murray (the spelling, J-o-r-d-*o*-n is incorrect)

Page 425, MacCraken, Walter H. (the spelling, M-a-c-C-r-a-*c*-k-e-n is incorrect)

OBITUARIES

DR. JOHN L. CHESTER

Dr. John L. Chester (Fellow) of Detroit, Michigan, died May 31, 1937.

Dr. Chester was born in New York State, but came with his family to Michigan at an early age. He received his medical degree from Saginaw Valley Medical College in 1901, and started practice in Emmet, Michigan. In 1917, he moved to Detroit and practiced there until the time of his death, confining his practice to Internal Medicine. His work was largely in the field of cardiology, on which subject he published a number of papers.

Dr. Chester held staff positions at Providence Hospital (Chief-Elect), and at Seymour Hospital, Eloise, in which institution he was Physician in Chief, Division of General Medicine. He was active in teaching, and held appointment as Professor of Clinical Medicine in Wayne University College of Medicine. He was a Fellow of the American College of Physicians since 1926.

Dr. Chester was a very earnest student in his field, and his death will be a great loss to his large practice, as well as to the profession. He was active in all local medical society activities, read many papers before medical groups, and took a particularly keen interest in the internes and younger members of the profession, whom he was always ready to help with counsel and advice. The profession has lost an able clinician and a good friend.

HENRY R. CARSTENS, M.D., F.A.C.P.,
Governor for Michigan

DR. ISAAC IVAN LEMANN

Dr. Isaac Ivan Lemann (Fellow, 1920) of New Orleans, who was born at Donaldsonville, Louisiana, 1877, and died on September 2, 1937, will be sadly missed not only by the members of the medical profession of New Orleans and the State of Louisiana but by his many friends and admirers throughout the Nation.

Dr. Lemann was gentle and modest in his relations with other members of the profession. He was especially considerate and charitable toward the younger members of his profession. He was admired and loved by the student bodies of the institutions with which he was connected. Dr. Lemann made many valuable contributions to medical literature; outstanding among these was his work and published papers on diabetes. He was recognized as a clinician of superior ability, and personally a most lovable individual.

Dr. Lemann received the A.B. degree from Tulane University in 1895, A.B. from Harvard University in 1896, M.D. from Tulane University of Louisiana School of Medicine in 1900. Instructor in Clinical Medicine, Tulane University of Louisiana School of Medicine, 1906–1910; Assistant

Professor of Clinical Medicine, Tulane University of Louisiana School of Medicine, 1910–1914; Professor of Clinical Medicine, Tulane University of Louisiana School of Medicine, 1914–1937; Chief of Medical Service, Touro Infirmary, New Orleans; Consultant in Medicine, Charity Hospital, New Orleans; Senior Consultant in Medicine, Flint Goodridge Hospital of Dillard University; Vice Chairman of the Section on Practice of Medicine, American Medical Association, 1932–1933; Fellow of the American College of Physicians since 1920; Member, Orleans Parish Medical Society, Louisiana State Medical Society, American Medical Association, Southern Medical Association, American Society of Tropical Medicine, Southern Interurban Clinical Club, Association of American Physicians, and the American Clinical and Climatological Association.

The College has suffered a severe loss in the passing of Dr. Lemann and he will be sorely missed as a Member of the faculty of Tulane University and in relation to his hospital connections.

J. E. KNIGHTON, M.D., F.A.C.P.,
Governor for Louisiana

DR. HARRY GILMER WALCOTT

Dr. Harry Gilmer Walcott (Fellow, 1928), aged sixty, a native Texan, died June 2, 1937, in a Dallas hospital after a long illness.

Dr. Walcott was a descendant of pioneer Texas stock. His academic education was obtained at Austin College in Sherman, Texas, and the Holbrook Normal School in Tennessee. In 1901 he graduated with high honors from the Baltimore Medical College, where he remained as Associate Professor of Physiological Chemistry for one year. He then returned to his old home at Honey Grove, Texas, where he engaged in practice until April 1903, when he went to Chicago for a period of study under an association with the late Dr. Fenton B. Turck. While in Chicago Dr. Walcott gave particular attention to the study of disorders of digestion. Later in 1903 he moved to Dallas, Texas, to enter the practice of gastro-enterology. He was the first physician in the state to practice this specialty exclusively, and was throughout the years a recognized leader in his section. For a period of years he was professor of gastro-enterology in Baylor Medical School, and at the time of his death was an emeritus professor. Perhaps to Dr. Walcott more than to any other person belongs the credit for the placing of gastro-enterology on a high plane in Texas.

During the World War he served with distinction as a Captain in the Medical Corps of the United States Army.

To those who knew him best Dr. Walcott exemplified and practiced the highest ethical tenets of the profession. He was zealous of the welfare of his patients, affectionate and indulgent with his family, a loyal friend and a wise counselor to those who sought his opinion and advice.

He is survived by his wife, a son, Harry Gilmer Walcott, Jr., and a daughter, Mrs. William Lipscomb.

CHARLES T. STONE, M.D., F.A.C.P.,
Governor for Texas

DR. ELIJAH LUMBIA MASON

Dr. Elijah Lumbia Mason was born February 25, 1871, in Rocky Mount, Virginia, the son of Gilbert and Susan Goode Mason, of Virginia. He was educated in private schools. He was a resident of the District of Columbia since 1894. He was graduated in pharmacy from the National College of Pharmacy, 1896; and was graduated in medicine from Columbian (now George Washington) University, 1901.

Dr. Mason was married to Viola V. Hines of Virginia in 1906, and they had one child, Jack Wellons Mason. His wife and son survive him.

Dr. Mason was a member of the following organizations: Fellow of the American Medical Association; Fellow of the American College of Physicians; Medical Association of the District of Columbia, April 2, 1902; Medical Society of the District of Columbia, October 1, 1902 (Seniority Number 298); the Hippocrates-Galen Society, of which he was a past president; the Phi Sigma Kappa Fraternity. He was consulting physician to the Washington City Orphan Asylum, and to the Episcopal Eye, Ear and Throat Hospital. He was associate in Medicine of the Garfield Memorial Hospital.

He was connected with the Children's Hospital as pharmacist and after graduation in medicine as resident physician and pathologist.

On September 5, 1932, following an accident at Gallinger Municipal Hospital, he was totally incapacitated for practice. He died on August 30, 1937, as the result of bronchopneumonia.

It is difficult to draw any valid conclusions from such meager data, as to the character and life of Dr. Mason. But from those who came in contact with him for the more than forty years of his activities in Washington the record can be fully made up. Quiet and courteous in his dealings with others; conscientious and thorough in his professional work; gracious and kindly with his friends; always a gentleman. Such characters are an inspiration to those coming in contact with them, and to those coming after. His passing is a distinct loss to the profession.

V. B. JACKSON, Chairman;
J. D. THOMAS and F. R. HAGNER,
Committee

(Presented before the Medical Society of the District of Columbia, November 10, 1937.)

Medical Library

ANNALS OF INTERNAL MEDICINE

PUBLISHED BY

The American College of Physicians

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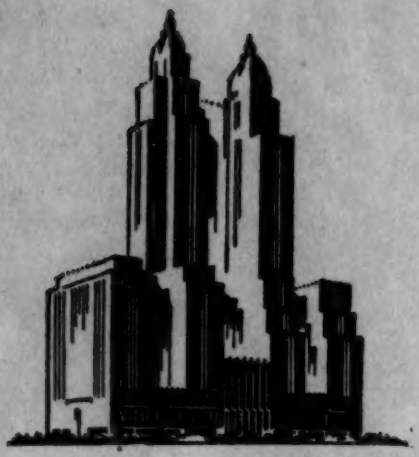

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ANNALS OF INTERNAL MEDICINE

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MANUSCRIPTS. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. DOE, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

REPRINTS. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

REVIEWS. The ANNALS will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

SUBSCRIPTION. This periodical is issued monthly, new volumes beginning with the July number each year. Subscriptions may be by the volume or year, but the volume basis is especially recommended. Volumes will consist of approximately 1,400 pages. Subscription price per volume, or per annum, net postpaid: $7.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Porto Rico; $7.50, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.00. Members of the American College of Physicians receive the ANNALS OF INTERNAL MEDICINE as a part of their membership. Checks should be drawn to the order of W. D. STROUD, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

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